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MASTER THESIS

**Protocol for a comparative study assessing the efficacy of
topical Timolol in patients with open-angle glaucoma or
ocular hypertension and concurrent treatment with systemic
beta-blockers**

**Πρωτόκολλο συγκριτικής μελέτης για την
αποτελεσματικότητα της τοπικά χορηγούμενης Τιμολόλης σε
ασθενείς με γλαύκωμα ανοικτής γωνίας ή οφθαλμική
υπερτονία και σύγχρονη λήψη συστηματικής θεραπείας με β-
αδρενεργικούς αποκλειστές**

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1. SUMMARY

Purpose: Topical beta-blocking agents have been used for many years for IOP reduction and management of glaucoma. However, there are limited data about their efficacy in patients that receive oral beta-blockers concurrently. The aim of this study is to evaluate the efficacy and safety of timolol ophthalmic solution in this group of patients.

Methods: This is an observational, prospective, controlled study. 92 patients with glaucoma or ocular hypertension will be enrolled and assigned to two groups (46 patients per group), depending on their systemic beta-blocker treatment status. All patients will receive topical timolol maleate for IOP reduction for six months.

Endpoints: The primary endpoint is mean IOP reduction from baseline at six months for each group. Comparisons between groups will be made for heart rate, blood pressure, ocular and systemic symptoms as well.

Conclusion: The results of this study could provide essential information about the management of this category of patients and eventually help clinicians to choose more effective and safe treatments.

Σκοπός: Οι τοπικά χορηγούμενοι β-αποκλειστές χρησιμοποιούνται εδώ και πολλά χρόνια για την μείωση της ΕΟΠ και την αντιμετώπιση του γλαυκώματος. Εντούτοις, τα δεδομένα είναι περιορισμένα για την αποτελεσματικότητά τους σε ασθενείς που λαμβάνουν ταυτόχρονα συστηματικούς β-αποκλειστές. Ο σκοπός αυτής της μελέτης είναι η αξιολόγηση της αποτελεσματικότητας και της ασφάλειας της χορήγησης οφθαλμικού διαλύματος τιμολόλης στη συγκεκριμένη ομάδα ασθενών.

Μέθοδοι: Πρόκειται για μια προοπτική, ελεγχόμενη μελέτη παρατήρησης. 92 ασθενείς με γλαύκωμα ή οφθαλμική υπερτονία θα συμμετέχουν στη μελέτη και θα κατανεμηθούν σε δυο ομάδες (46 ασθενείς ανά ομάδα) ανάλογα με το ιστορικό λήψης συστηματικών β-αποκλειστών. Όλοι οι ασθενείς θα λάβουν θεραπεία με τοπική τιμολόλη για μείωση της ΕΟΠ για έξι μήνες.

Καταληκτικά σημεία: Το βασικό καταληκτικό σημείο είναι η μέση μείωση της ΕΟΠ από την έναρξη στους 6 μήνες στις δυο ομάδες. Συγκρίσεις μεταξύ των ομάδων θα γίνουν ως προς τους καρδιακούς παλμούς, την αρτηριακή πίεση, τα οφθαλμικά και συστηματικά συμπτώματα.

Συμπέρασμα: Τα αποτελέσματα αυτής της μελέτης θα μπορούσαν να προσφέρουν σημαντικές πληροφορίες για την διαχείριση της συγκεκριμένης κατηγορίας ασθενών και ενδεχομένως να βοηθήσουν τους ιατρούς να επιλέγουν πιο αποτελεσματικές και ασφαλείς θεραπείες.

2. INTRODUCTION

2.1 Background

Glaucoma is a major public health issue. It is the second leading cause of global blindness and the most common cause of irreversible blindness (1). It had been estimated that approximately 8.4 million people were bilaterally blind from glaucoma in 2010 (2). Global prevalence of open-angle glaucoma (OAG), which is the most common type, varies from 2.2% to 3% according to recent studies (3, 4). Moreover, a large population based study in northern Greece estimated the prevalence of OAG in Greek population at 5.5% (5).

According to European Glaucoma Society: "The open-angle glaucomas are chronic, progressive optic neuropathies that have in common characteristic morphological changes at the optic nerve head and retinal nerve fibre layer in the absence of other ocular disease and congenital anomalies. Progressive retinal ganglion cells death and visual field loss are associated with these changes" (6). Several factors have been associated with higher risk of OAG development or progression. Intraocular pressure (IOP) is one of the most important risk factors. Although high IOP is not essential for the diagnosis of glaucoma and not included in the current glaucoma definition, it is the only factor to date that could be modified as part of glaucoma management. Two large randomized controlled trials provided evidence that decreasing IOP in patients with ocular hypertension could be beneficial for the prevention of OAG (7, 8). Moreover, the Early Manifest Glaucoma Trial (EMGT) suggested that a 25% decrease from baseline IOP could reduce the risk of OAG progression by 50% in treated patients (9).

The aim of glaucoma management currently is IOP lowering. This can be achieved by topical or systemic medication and surgical or laser therapies. Topical medication is the treatment of choice for patients with early and moderate glaucomatous damage. There are several agents currently available for topical administration including beta-receptor antagonists, prostaglandin analogues, carbonic anhydrase inhibitors, alpha2 selective adrenergic agonists and parasympathomimetics. Beta-blockers were the most widely used agents but lately prostaglandin analogues have become first-line therapy of glaucoma. However, topical beta-blockers are still administered to a large proportion of patients especially as part of fixed combination preparations.

2.2 Timolol maleate

Timolol maleate is a non-selective beta-adrenergic blocker that was introduced in 1970s. It does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Katz et al were the first to describe that a single drop of 0,5% to 1,5% of this drug applied topically produced rapid and prolonged lowering of IOP in normal eyes (10). Timolol, like other topical beta-blockers, can lower IOP by decreasing the formation of aqueous humor by the

ciliary body. Experimental evidence indicates that timolol could act as a beta-adrenergic antagonist in anterior uveal tissue (which apparently contains beta-adrenergic receptors). This could inhibit sympathetic tone to the ciliary processes which stimulates the formation of aqueous humor (11). The precise mechanism of hypotensive mechanism of timolol has not been established yet.

Several studies have provided evidence about the safety and efficacy of timolol and beta-blockers in patients with glaucoma. The mean reduction from baseline IOP is approximately 20% to 25% but the drug seems to have its maximum effect during waking hours (12, 13). Topically administered beta-blocker agents are generally well tolerated by patients and few ocular side-effects have been reported including corneal hypesthesia. However, systemic side effects are much more significant and potentially life threatening in rare cases. Although the agent is administered topically, it may gain access to the systemic circulation through the lacrimal system or through the conjunctival vessels. Blood levels that can be achieved by instillation of beta-blocker drops are not as high as those following oral administration but may produce serious side effects to predisposed patients (14). Therefore, a full medical history report is essential before this type of medicine is prescribed. Contraindications include asthma, severe chronic obstructive pulmonary disease, bradycardia, second or third-degree heart block and congestive heart failure. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function. Moreover, beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Other categories of reported side-effects include nervous system problems such as hallucinations or depression and dermatological problems (alopecia).

There are many medicinal products containing timolol maleate commercially available, most of them in the form of ophthalmic solution and 0.25% or 0.5% concentration. Common brand names are Timoptic (Bauch&Laumb), Temserin (Vianex), Yesan (Rafarm) and the ophthalmic gel preparation Geltim (Laboratoires Thea). Moreover, timolol maleate 0.5% is used in almost every fixed combination preparations currently usually combined with a carbonic anhydrase inhibitor. The suggested dosage of timolol maleate 0.25% and 0.5% is one drop instillation in the eye twice daily.

2.3 Oral beta-blockers and patients with glaucoma

Patients with glaucoma are usually elderly and frequently face co-existing systemic conditions. Data from a retrospective study that examined the medical records of 100 patients with OAG suggest that 84% of the patients had one or more systemic disorders (15). Systemic hypertension was the most common disorder and approximately 20% of all patients received oral beta-blocking agents.

Oral beta-blockers are used mainly in the management of hypertension, arrhythmias and angina pectoris. As mentioned before, the target of these agents is the beta-adrenergic receptors which are found within the sympathetic nervous system. There are three subclasses of beta receptors. Beta1 receptors are found in heart muscle and kidney and when stimulated they increase heart rate and contractility and cause release of renin from kidneys. The location of beta2 receptors is in smooth muscle causing bronchodilation in the lungs and vasodilation in skeletal and cardiac muscle upon stimulation. Beta3 receptors are found in fat cells. Beta-blocking agents are categorized as selective (affecting only beta1 receptors) and non-selective (affecting both beta1 and beta2 receptors).

Systemic beta-receptor blockade could have an impact on IOP as well. It has been recently reported that oral beta-blockers may lower IOP by approximately 1mmHg in patients with no history of medical treatment for glaucoma (16). Concurrent administration of topical and oral beta-blocking agents raises safety and efficacy questions. In 1979, Batchelor et al. reported no drug interaction or additive effect in a small group of patients receiving timolol topically and orally (17). However, a retrospective study in 1992 and a post-hoc analysis of data collected from two randomized controlled trials in 2000 suggest that the ocular hypotensive effect of topical beta-blockers in glaucoma patients receiving oral beta-blockers is significantly lower compared to patients that do not receive oral medication (18, 19). In the second study, one of the topical agents that were examined was timolol maleate 0.5% and the difference of mean IOP reduction between the two groups was estimated at 1.6mmHg. The precise mechanism responsible for this interaction is not clear but it has been suggested that chronic systemic beta-blocker administration could result in ciliary body beta-receptor blockade reducing the efficacy of topically administered agents. Another possible mechanism could be beta-receptor desensitization.

2.4 Rationale for the study

Topical beta-blockers are still widely prescribed for the management of glaucoma. Additionally, during the past few years fixed combination preparations have become a popular choice for treatment as they offer the advantage of two IOP lowering agents in a single drop and almost all of them contain timolol maleate. Moreover, patients with glaucoma often receive treatment for other coexisting conditions. Consequently, concurrent topical and oral administration of beta-blockers is not a rare phenomenon. In fact, an Australian study in 2007 estimated that approximately 20% of patients with glaucoma received both topical and oral beta-blocking agents (20). Unfortunately, it is not clear whether the efficacy of topical agents is affected in these patients. Limited data from previous reports suggest reduced IOP lowering effect but further research is needed. The aim of this study is to

examine the efficacy and safety of topical timolol in patients that already receive systemic beta-blocking agents. This could provide essential information about the management of this category of patients and eventually help clinicians to choose more effective and safe treatments.

3. STUDY OBJECTIVES

Primary objective

To evaluate the IOP lowering efficacy of topically administered timolol maleate in patients with previously untreated OAG or ocular hypertension and concurrent treatment with systemic beta-blocking agents, compared to patients that do not receive systemic beta-blockers, during a follow-up period of six months.

Secondary objectives

- Evaluation of blood pressure and heart rate
- Evaluation of ocular discomfort (burning and stinging symptoms) and subjective systemic symptoms

4. STUDY DESIGN

This is an observational, prospective, controlled study for timolol maleate in newly diagnosed and previously untreated patients with OAG or ocular hypertension. A total number of 92 patients will be enrolled and assigned to two groups (46 patients per group), depending on their systemic beta-blocker treatment status. Patients who receive oral beta-blockers will be assigned to the first group and patients who do not report recent beta-blocker treatment will be assigned to the second group which is the control group. The groups will be matched for age and sex in order to minimize confounding factors. The matching ratio will be 1:1. All patients will start receiving topical timolol maleate 0.5% drops twice daily for the management of elevated IOP and will be followed up for 6 months. The initiation of this treatment for each patient will be based on ophthalmologist's decision according to the clinical practice.

5. ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Subjects must meet all the following criteria to be eligible for enrolment into the study:

- Age over 45 years
- Exhibition of characteristic glaucomatous optic disc damage and visual field loss or glaucoma suspect with high risk of glaucoma development (upon investigator's judgement)
- Untreated baseline IOP of 21mmHg or greater and less than 30mmHg in each eye and IOP difference within 5mmHg between patient's eyes (enrolment IOP must be verified by two separate measurements)
- No medical history of previous ocular surgery (including laser) except uncomplicated phacoemulcification for cataract extraction performed at least 6 months before enrollment
- Open angle in anterior chamber verified by gonioscopy (grade 3 or 4 of Schaffer classification)
- Best corrected visual acuity of 3/10 or better in each eye (Snellen)
- Current treatment with oral beta-blocking agents initiated at least 6 months before the study enrolment (for patients assigned to first group)
- Signed informed consent

5.2 Exclusion criteria

Subjects that meet at least one of the following criteria will not be included in the study:

- Medical history of conditions that are contradicted for beta-blocker administration (asthma, severe chronic obstructive pulmonary disease, bradycardia, second or third-degree heart block and congestive heart failure)
- Any type of glaucoma other than primary open-angle glaucoma
- Active external ocular disease, severe dry eye, corneal abnormalities and any other condition that could affect the reliability of Goldmann applanation tonometry

- History of infectious ocular disease, late stage macular degeneration, severe diabetic retinopathy or signs of macular oedema
- History of uncontrolled systemic disease (i.e. hypertension or diabetes)
- Central corneal thickness $\leq 500\mu\text{m}$ or $\geq 600\mu\text{m}$
- History of any ocular medication (except artificial tears) 1 month before enrolment and contact lens users
- History of chronic systemic steroid medication
- History of oral beta-blocking treatment (for patients in control group)
- History of allergic reaction, hypersensitivity or any adverse event to the study medication
- Female patients of childbearing potential
- Vertical cup to disk ratio ≥ 0.8
- Mean deviation (MD) worse than -12dB and sensitivity less than 15dB in the 5 central degrees of both hemifields in Humphrey 24-2 SITA standard perimetry (advanced glaucomatous visual field loss)
- Patients who had participated in a drug research study within 30 days before study initiation

Subjects that are unable to understand the study procedures or give informed consent will be excluded from participation. Any other reason for patient exclusion is upon primary investigator's judgement.

6. STUDY PROCEDURES

6.1 Enrolment process

Patients visiting the outpatient clinics of 1st Department of Ophthalmology in AHEPA University Hospital of Thessaloniki will be pre-screened and appointed for an eligibility screening visit. During this visit, patients will undergo a detailed ophthalmologic examination and their medical history will be recorded. Optic disc imaging and a reliable 24-2 SITA standard visual field test will be performed (Humphrey Visual Field Analyzer; Carl Zeiss Meditec Inc.). Heart rate and blood pressure will be measured as well.

6.2 Procedures, treatment and follow-up

Eligible subjects will be appointed for 24h IOP monitoring in ophthalmology clinic and IOP fluctuation will be recorded. Patients' IOP will be measured at 06:00, 10:00, 14:00, 18:00, 22:00 and 02:00 (± 30 min). In the next morning at 10:00 (baseline visit), IOP, blood pressure and heart rate will be measured again and these will be patient's baseline measurements. After informed consent is signed, patients will be instructed how to use the study medication properly. All subjects will receive 1 drop of timolol maleate 0.5% sterile ophthalmic solution (Temserin, Vianex A.E.) in each eye every 12 hours starting from the day of baseline visit. Patients will be encouraged to use the drops at specific hours of the day (09:00 ± 30 min and 21:00 ± 30 min). Patients who receive oral beta-blocking agents (selective or non-selective) will be assigned to group 1 and this treatment will remain unchanged during the study. The rest of the patients will be assigned to group 2 (control group). Visit 1 will take place 1 month later and patients response to the study drug will be evaluated. The anticipated IOP lowering effect of timolol is 20% to 25% from baseline. The IOP will be measured and recorded at 8:30 ± 30 min (before morning instillation) and at 11:00 ± 30 min (approximately 2h after instillation) and blood pressure and heart rate measurements will be recorded. This will be repeated 3 months (visit 2) and 6 months (visit 3) after the initiation of the treatment. Visit 3 will be the final visit and a visual field test and 24h IOP monitoring will be repeated. During all visits patients will undergo a detailed ophthalmologic examination and will be questioned about subjective ocular and systemic symptoms. After the end of the study patients will continue a follow-up schedule according to the stage and progression of their disease.

6.3 Endpoints assessment

Intraocular pressure

IOP will be measured using calibrated Goldmann applanation tonometry (mmHg units) by clinicians masked to patients' medical history and previous measurements.

Heart rate and blood pressure

Heart rate and blood pressure will be measured using a calibrated automatic electronic sphygmomanometer (beats per minute and mmHg). The same masking procedure will be applied in this case as well.

Ocular discomfort

Ocular discomfort will be evaluated using the ocular surface disease index (OSDI) questionnaire which includes 12 questions and a 5-scale grading system (0 to 4) (Walt et al, 1997)

Subjective systemic symptoms

Subjective symptoms will be evaluated by a 4-scale grading questionnaire ranging from “no”, “mild”, “moderate” to “severe” symptoms (0 to 3). It will include questions about general malaise, headaches, fatigue and other symptoms.

6.4 Subject withdrawal

Subjects are free to withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety or behavioural reasons (i.e. rapid disease progression, treatment non-compliance). Necessary efforts should be made to document subject's course, outcome and potential adverse events, if possible. The investigator is responsible for inquiring the reasons for withdrawal. If the subject withdraws from the study, no further evaluations should be performed and no additional data should be collected. Any data collected before withdrawal of consent can be retained by the investigator/sponsor and used for study purposes.

7. STATISTICAL ANALYSIS AND CONSIDERATIONS

7.1 Study endpoints

The primary endpoint is the difference between mean IOP reduction in group 1 (receiving oral beta-blockers) and mean IOP reduction in group 2 (control group) after six months' treatment with topically administered timolol maleate 0.5% ophthalmic solution. For each patient, both eyes will be included in the analysis.

Secondary endpoints are difference of mean heart rate and blood pressure and difference of mean scores for ocular discomfort and systemic symptoms between the 2 groups at the end of the study.

7.2 Sample size calculation

As previously mentioned, the primary endpoint of this study is a comparison of mean IOP reduction between the two groups. Therefore, this difference will be tested using a t-test at P-value (significance level) $P=0.05$. In a similar study in 2000, Schuman et al estimated this difference at 1.6mmHg (less reduction for patients taking beta-blockers) with a standard deviation for the control group $s=2.6$. The degree of certainty (power of the study) to detect the difference as significant in our study will be 80%. The parameters for sample size calculation are the following:

$\Delta=1.6$	$s=2.6$
$\text{Alpha}=0.05$	Critical $t=1.96$
$\text{Beta}=0.2$	Power=0.8

Sample size will be calculated according to parameters above and using the following type:

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(2.6^2 + 2.6^2/1)(1.96 + 0.84)^2}{1.6^2}$$

$$n_1 = 41$$

$$n_2 = K * n_1 = 41$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means

σ_1, σ_2 = variance of mean #1 and #2

n_1 = sample size for group #1

n_2 = sample size for group #2

α = probability of type I error

β = probability of type II error

z = critical Z value for a given α or β

k = ratio of sample size for group #2 to group #1

The result is 41 patients per group or 82 patients in total. However, we should anticipate a drop-out rate of approximately 10%, so the final sample size will be:

$n=92$ patients in total or 46 patients per group

7.3 Statistical analysis

Mean IOP reduction will be calculated for each group (final IOP - baseline IOP). A per protocol analysis will be followed, so subjects that will withdraw from the study will not be included in the analysis. As previously mentioned, IOP will be recorded twice during each visit, before and after morning instillation (trough and peak drug effect). Therefore, two separate analyses will be performed, one for final trough and one for final peak measurement. For the analysis of the primary endpoint, an independent samples t-test with significance level $P=0.05$ will be performed. The same test will be used for the comparison of mean heart rate and blood pressure change. Demographic characteristics will be presented using descriptive statistics and compared between groups. The scores for ocular discomfort and systemic symptoms for each group at final visit will be transformed into dichotomous variables (severe – not severe) and compared using a χ^2 test. The software that will be used is IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp.).

8. ADVERSE EVENTS

8.1 Adverse event definition

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device: the event needs not necessarily to have a causal relationship with the treatment or usage. Adverse events may include:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression of underlying disease

Additionally, they may include signs or symptoms resulting from:

- Drug overdose
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure during pregnancy

8.2 Adverse event reporting

All observed adverse events regardless of suspected causal relationship to study medication (timolol maleate) will be recorded. For all adverse events, the ophthalmologist must search and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event. For adverse events with a causal relationship to timolol, follow-up is required until the event resolves or stabilizes at a level acceptable to the ophthalmologist. For serious adverse events, the reporting period begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, through the entire study period or 1 month after the last administration of timolol within the observational period.

9. ETHICS

This study will be conducted in compliance with the protocol, the ethical principles set forth in the Declaration of Helsinki, the ICH Guideline E6 for GCP and applicable regulatory requirements. Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting research studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

9.1. Institutional Review Board/Independent Ethics Committee

The protocol and any amendments, the subject informed consent and any information on compensation for study-related injuries or payment to subjects, will receive IRB/IEC approval prior to initiation of the study. During the study, the investigator will send to the IRB any reports of adverse events that are serious, unlisted and associated with the investigational drug and any new information that may adversely affect the safety of the subjects or the conduct of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task.

9.2. Informed consent

Before a subject's participation in the study, investigator is responsible for obtaining freely given consent, in writing, from the subject or a legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. The written informed consent form and any other written information to be provided to subjects should be revised whenever new information becomes available that may be relevant to the subject's consent. Subjects unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding. If a subject or a subject's legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. Subjects may withdraw consent from participation in the study at any time. In the event a subject withdraws consent to receive study drug, the site may (with the subject's agreement) continue to contact the subject, general practitioner, and any other physician or medical care provider for the collection of outcome and survival follow-up data.

9.3. Subject confidentiality

The investigators and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. The investigator must ensure that the subject's anonymity is maintained. Sponsor personnel whose responsibilities require access to personal data should agree to keep the identity of study subjects confidential.

10. COMMITTEES

Executive Committee

The Executive Committee (EC) consists of members of the academic leadership of the study. The EC will be responsible for the conduct of the study including addressing any Data Monitoring Committee recommendations and overseeing publication of the results.

Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will monitor the progress of the study and ensure that the safety of subjects enrolled in the study is not compromised. This committee will review accumulating data on a regular basis, and may request to review partially unblinded data. The DMC will make recommendations to the Executive Committee regarding the safety of subjects currently enrolled and yet to be enrolled in the study.

Clinical Endpoint Committee

The Clinical Endpoint Committee (CEC), composed of experts in the relevant fields, will review all reported study outcomes to provide consistency and validity in the assessment of outcomes. Their decisions will be based on blind clinical data and will be used for the final statistical analyses.

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