INTERMITTENT EXOTROPIA STUDY 5 (IXT5)

A Randomized Clinical Trial of Overminus Spectacle Therapy for Intermittent Exotropia

PROTOCOL

Version 3.0
November 22, 2019

PROTOCOL AMENDMENT II (11-22-19)

Note that changes to the original (18-month) protocol (protocol changes #1 through #5) are incorporated throughout the protocol. The 18 to 36 month extension study protocol (protocol change #6) is detailed at the end of this protocol amendment II.

Protocol Change #1 – Discontinue weaning overminus lens treatment between 12-15 months

Original Protocol

A three-month period of weaning of overminus consisted of prescribing the overminus group subjects -1.25D overminus (half of the -2.50D prescribed at randomization) at the 12-month visit and wearing this correction until discontinuing the overminus completely at the 15-month visit. The purpose of weaning overminus as opposed to discontinuing overminus abruptly was to potentially help retain the effect of the overminus off treatment.

Changed Protocol

At the 12-month visit, subjects in the overminus treatment group will have overminus treatment discontinued immediately, without weaning. These subjects will be prescribed the non-overminus spectacles they would have been prescribed at 15 months in the original protocol (section 2.6.1).

The flow chart in section 1.17 has been updated. Section 4.3.2 on risks of overminus was also updated.

Relevant additions to the analysis plan:

- Because weaning may increase the retention of the treatment effect once off treatment, discontinuing the weaning may decrease the off-treatment effect observed at 18-months. For this reason, the 18-month off-treatment analyses will be performed using 1) the full cohort, and 2) a cohort limited to subjects who were prescribed weaning between 12 to 15 months (i.e., prior to weaning being discontinued per Protocol Amendment II) (see modifications to section 5.2).
- In addition, 18-month distance control and change from baseline will be tabulated by treatment group according to prescribed weaning status (i.e., full, partial, or no prescribed weaning) (section 5.3.2.2).

Rationale

The Data Safety Monitoring Committee (DSMC) concluded on 10/25/19 that progression of myopia is occurring more frequently in subjects treated with overminus spectacles compared to non-overminus spectacles. Between baseline and 12 months, the mean change in spherical equivalent refractive error at 12 months was -0.42 D (diopter) in the overminus group and -0.05 D in the non-overminus group (difference = 0.39 D P = <.0001). The proportion of subjects whose spherical equivalent refractive error changed by more than 1.00D was 17% in the overminus group (29 of 168); and 2% in the non-overminus group (3 of 146). The DSMC recommended that all subjects active in the full treatment* or weaning phases in both treatment groups be asked to come in for a visit as soon as possible to be given the new information, complete their pending follow-up visit, receive study-paid non-overminus glasses (regular

glasses or no-correction glasses) to be worn through 18 months, and be invited to continue in the study after 18 months to be treated at investigator discretion and to return for visits at 24 and 36 months.

*Note that the protocol does not require amending the 0 to 12-month on-treatment period in order to discontinue full overminus treatment given that the 37 remaining 12-month visits (as of 11/5/19) were planned to occur by December 2019. These 12-month visits will be completed only slightly early (all subjects have ≥9 months of treatment). As detailed above, non-overminus glasses will be prescribed between 12 and 18 months.

Protocol Change #2

Original Protocol
A lens change was required at the 15-month visit in both treatment groups to allow for discontinuation of half-strength (-1.25D) overminus spectacles in the overminus group. The 15-month glasses prescription is the same as the non-overminus group has received throughout the protocol.

Changed Protocol
The 15-month spectacle prescription is the same as in the original protocol (i.e., non-overminus for both treatment groups), but *whether a patient needs to receive a change in spectacles at 15 months to achieve this prescription* depends on whether their spectacles had been changed to non-overminus at the 12-month visits occurring after Protocol Amendment II.

Section 2.6.1 on treatment in the **overminus** group has been revised as follows:

15-Month*
- If the 12-month spectacles for a subject were issued **before** Protocol Amendment II and therefore contain partial-strength overminus (-1.25D), they should be changed to non-overminus lenses at the 15-month visit to discontinue the overminus treatment.
- If the 12-month spectacles for a subject were issued **on/after** Protocol Amendment II and therefore are already non-overminus spectacles, the non-overminus spectacles should be continued at the 15-month visit.

**Unless the subject has already met deterioration criteria confirmed by masked examiner as described in section 3.7, in which case spectacles are prescribed at investigator discretion.*

Section 2.6.2 on treatment in the **non-overminus** group has been revised as follows:

15-Month*
- If the 12-month spectacles for a subject were issued **before** Protocol Amendment II and, the non-overminus lenses should be replaced with new non-overminus spectacles at the 15-month visit, to maintain masking of treatment groups.
- If the 12-month spectacles for a subject were issued **on/after** Protocol Amendment II and therefore are already non-overminus spectacles, the non-overminus spectacles should be continued at the 15-month visit. There is no longer a reason to change the glasses to maintain masking, given that both treatment groups would already be wearing non-overminus glasses in this situation.

**Unless the subject has already met deterioration criteria confirmed by masked examiner as described in section 3.7 in which case spectacles are prescribed at investigator discretion.*

Rationale for Change
Whether glasses need to be changed at 15-months depends on when each subject's 12-month glasses were issued, before or on/after Protocol Amendment II. See details in changes to protocol (above).

Protocol Change #3

Original Protocol
Cycloplegic refraction and autorefraction were not performed at the 18-month visit.

Changed Protocol
Cycloplegic refraction will be performed at the 18-month visit, and autorefraction will be mandatory if an autorefractor is available at the site (section 3.4). Analysis of 18-month refractive error data was added to section 5.4.1.

Rationale for Change
Given the increased myopia progression in the overminus lens group, the 18-month visit is the first opportunity to assess whether the overminus group continues to have higher myopia than the non-overminus group or whether the two treatment groups start to become similar once treatment is discontinued.

Protocol Change #4

Original Protocol
Cycloplegic axial length and additional biometry were not measured in the study.

Changed Protocol
Cycloplegic axial length, flat corneal radius, anterior chamber depth, and lens thickness (if available) will be measured at 18-months (section 3.4). Analyses for this data are described in section 5.3.1.5 and 5.3.1.6

Rationale for Change
Given the increased myopia progression in the overminus lens group, the study is interested in whether axial length also differs between treatment groups.

Protocol Change #5

Original Protocol
Study-paid spectacles (lenses and frame) were provided at the 12-month visit and a change of lenses was provided at the 15-month visit.

Changed Protocol
Study-paid spectacles (frames and lenses) will be provided at 12 months, 15 months and 18 months (section 4.7)

Rationale for Change
Paying for a full set of spectacles at the 15-month visit will enable the study to offer a full set of spectacles to all patients coming in for early visits to have treatment discontinued. Study-paid

spectacles will be provided at 18 months now that cycloplegic refraction is being performed to check the spectacle prescription at that time.

Protocol Change #6

Original Protocol
The study ends with the 18-month visit.

Changed Protocol *(also see next page)*
This Protocol Amendment allows for an extended follow up period from the 18 to 36 months after randomization. All patients enrolled in IXT5 will be invited to participate, regardless of whether they are still active in the 18-month study. *See specifications on next page.*

Rationale for Change
Given the higher rate of myopia progression observed in overminus group vs. non-overminus group between randomization and 12 months, the goal is to determine whether the overminus group continues to have higher myopia than the non-overminus group or whether the two treatment groups will have similar myopia progression over the long term.

PROTOCOL AMENDMENT II (11-22-19) PROTOCOL CHANGE #6 (CONTINUED) EXTENDED FOLLOW UP BETWEEN 18 TO 36 MONTHS

This protocol change allows for an extended follow up period 18 to 36 months after randomization.

Objective

To compare long-term refractive error between subjects originally treated with either overminus spectacles or non-overminus spectacles as part of the 18-month randomized trial.

Protocol Specified Follow-up Visits

Visits will occur at 24 months (±3 months) and 36 months (±3 months) from randomization.

Study Procedures/Data Collection

The following testing procedures will be performed in the following order: using similar methods as the 18-month visit except where noted.

1. Treatments used since the last visit
2. Visual acuity
   - Measured using the investigator's usual testing procedure using an optotype method.
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, visual acuity testing should be performed *with* prism.
     - If deliberate overminus* is currently prescribed, visual acuity testing should be performed *with* the overminus correction.
   - If visual acuity is 20/32 or worse (75 letters or less) in either eye, a manifest refraction must be performed. If the examiner believes that the patient's current correction is not optimal, trial frames with new correction should be used for all testing at the visit. This includes testing visual acuity again, with the patient wearing trial frames.
3. Control of the Exodeviation #1 **- masked**
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, testing should be performed *without* prism.
     - If deliberate overminus** is currently prescribed, testing should be performed in trial frames *without* the overminus component of the prescription.
4. Stereoacuity Testing – **- masked** stereoacuity is tested only once, with no repeat testing on the same day or a subsequent day.
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, stereoacuity testing should be performed *with* prism.
     - If deliberate overminus** is currently prescribed, stereoacuity testing should be performed *with* the overminus correction.
5. Control of the Exodeviation #2 – **masked** see details under Control Testing #1 above
6. Cover Test and PACT Testing **- masked**
   - Testing must be performed in current refractive correction.
   - If prism is currently prescribed, ocular alignment testing should be performed *without* prism.
   - If deliberate overminus** is currently prescribed, ocular alignment testing should be performed in trial frames *without* the overminus component of the prescription.
7. Control of the Exodeviation #3 – **- masked** see details under Control Testing #1 above

8. Assessment of Deviation Throughout Exam**- masked**
9. Cycloplegic Refraction
11. Cycloplegic Autorefraction (mandatory if autorefractor is available at the site) as described in section 3.4
12. Cycloplegic Axial Length Measurement and Additional Biometry (mandatory if biometer is available at the site) as described in section 3.4
    - Axial length
    - Flat corneal radius
    - Anterior Chamber depth
    - Lens thickness, if available

*Deliberate overminus lenses = lenses that yield > 0.50 D *more minus* spherical equivalent (SE) than the refraction SE. Note that prescribing underplus or no plus is not considered deliberate overminus.

Steps #3 through #8 must be performed in order by a masked examiner who is a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

Treatment

After 18 months, IXT treatment (surgical, non-surgical, management of refractive error) is at investigator discretion.

Costs

The parent/guardian of each subject will be compensated $50 for completion of each of the 24-month and 36-month visits, up to a total of $100. If there are extenuating circumstances, and the subject is unable to complete the annual study visits without additional funds due to travel costs, additional funds may be provided.

The study will pay for visits specific to the research study, but will not pay for usual care visits that would occur whether or not the subject was in the study. The cost of usual care visits will be the responsibility of the subject or his/her insurance company.

The study will pay for a pair of spectacles (lenses and frames) at the first extension study visit (24 months or 36 months). Spectacle changes / new spectacles prescribed at other times will not be paid for by the study.

Treatment after 18-months is at investigator discretion and is not part of this protocol. Any costs associated with treatment will not be paid for by the study.

Risks

The procedures in this study are part of daily eye care practice in the United States and pose no known risks.

Subject Contact During Follow Up

Between annual visits, subjects may be called periodically by the Jaeb Center to promote retention.

Re-consenting of Subjects

An addendum to the original informed consent form (and addendum to the assent form, if required) for the extension study will be signed by parents who elect to continue their child's study participation. Re-consenting will occur at the next 12, 15, or 18-month randomized trial visit but could occur at other times either before or after participation in the 18-month trial has ended. A subject (and respective parent) may withdraw from the study at any time.

Statistical Analyses

The following analyses will be completed separately at the 24-month and 36-month visits to evaluate the effect of the overminus treatment approach followed by usual clinical care versus the non-overminus treatment approach followed by usual clinical care**:**

- Spherical equivalent refractive error will be compared between treatment groups using an ANCOVA model that adjusts for baseline spherical equivalent refractive error. The treatment group difference and a 95% confidence interval will be calculated.
- Mean distance control (average of 3 measurements) will be compared between treatment groups using an analysis of covariance (ANCOVA) model, which adjusts for baseline distance control, distance PACT, age, refractive error, and use of ADHD medication, to address potential residual confounding.
- The proportion of subjects with no spontaneous tropia will be compared between treatment groups as in section 5.1.2.1.
- Axial length, flat corneal radius, anterior chamber depth, and lens thickness (if available) will be compared between treatment groups as in section 5.3.2.3 and
- Secondary outcomes of near control, angle magnitude, and near stereoacuity will also be compared between treatment groups as in section 5.3.1.
- Treatments used since the last visit will be tabulated by treatment group.

PROTOCOL AMENDMENT I (11-8-16)

This amendment provides for the following protocol changes:

Protocol Change #1

Original Protocol

At the time of enrollment and each follow-up visit at 6, 12, 15, and 18 months, parents are asked to respond to a survey of symptoms potentially associated with spectacle treatment (headaches, eye strain, and other problems with spectacle wear) based on their observations of their child in the past 2 weeks.

Changed Protocol

1. To add a 7-question survey of intermittent exotropia symptoms to be administered to the child.
2. To add a health-related quality of life questionnaire to evaluate whether either treatment impacts the effect of intermittent exotropia on quality of life.
    - Children ages 5 and older at the time of enrollment will complete an 11-item questionnaire to assess how their eye condition affects their quality of life. Children 4 years of age and younger at the time of enrollment will not complete the child questionnaire.
    - A 16-item parental questionnaire will assess how the child's eye condition affects the quality of life of the parent (for all subjects).
3. The surveys and questionnaires will be completed at the time of enrollment; and at 6-month, 12-month, and 18-month follow-up visits.

Rationale for Change

There is value in determining how overminus treatment may impact the child's intermittent exotropia symptoms and the child's and parent's quality of life. Recently, a patient derived 7-question intermittent exotropia symptom survey has been developed for childhood IXT and, previously, a patient and parent derived HRQOL instrument has been developed specifically for IXT and used successfully in previous PEDIG IXT studies.

Protocol Change #2

Original Protocol

Both the 12-month on-treatment comparison of mean distance control and the 18-month off-treatment comparison of mean distance control are considered separate primary analyses, with each allocated 0.05 alpha.

Changed Protocol

The 12-month on-treatment comparison will be the sole primary analysis and the 18-month off-treatment comparison changed to a planned secondary analysis upon which sample size continues to be based.

Rationale for Change

The previous allocation of 0.05 alpha to both the 12-month on-treatment comparison and the 18-month off-treatment leads to an experiment-wise alpha of up to 0.10. Selecting one comparison as the primary analysis limits the experiment-wise alpha to no more than 0.05. Whether

overminus spectacles can improve control of exotropia after 12 months of treatment is the primary study question. The 18-month off-treatment analysis can be considered the secondary question. First, the overminus weaning schedule may require refinement before we can definitively determine the effect of overminus after treatment is discontinued. Second, an on-treatment effect would need to be seen at 12 months in order to potentially see an effect off-treatment at 18 months. Finally, clinicians who use overminus to delay another form of treatment, such as surgery, may be less interested in the off-treatment effect. Whether a benefit of overminus can be maintained off treatment, will still be addressed by the 18-month off-treatment comparison as a planned secondary analysis.

Protocol Change #3

Original Protocol

The primary analysis uses the observed 12-month visit data regardless of whether non-randomized treatment was prescribed. Subjects who are lost to follow up before the 12-month visit are excluded. The 18-month off treatment analysis was defined similarly.

Changed Protocol

The primary analysis (section 5.1) will be defined as follows:

- Subjects who are treatment crossovers (non-overminus group subjects who are prescribed overminus therapy; overminus group subjects who have overminus spectacles formally discontinued) will have their observed 12-month data analyzed provided they complete at least one distance control testing at the 12-month outcome exam; otherwise their average distance control score will be imputed using multiple imputation.
- Subjects who are prescribed IXT treatment *other than overminus or non-overminus refractive correction* (e.g. surgery, vision therapy, patching) will have their average distance control score imputed using multiple imputation, using data from all visits prior to the initiation of the alternative therapy. Multiple imputation will be used for these subjects regardless of whether any control testing is completed at the 12-month visit.
- Subjects who are lost to follow up before the 12-month visit will also have their outcome imputed using multiple imputation.

The original primary analysis is now an alternative analysis in section 5.1.1.1, along with the original alternative analysis. A third alternative analysis has been added to explore the effect of how treatment crossovers are handled in the primary analysis.

The secondary 18-month off-treatment analysis was changed in parallel (section 5.2).

Rationale for Change

For subjects who are prescribed treatment other than what they were randomized to (e.g. surgery, overminus spectacles, vision therapy) the 12-month visit data would reflect the effect of the non-randomized treatment they receive. If a higher proportion of subjects in the non-overminus group are prescribed a non-randomized treatment that is more effective than the overminus spectacles, the study might fail to detect an effect of overminus, if one exists. It was felt acceptable and conservative to analyze the observed 12-month data for treatment crossovers given that these subjects are receiving study treatments; however, it was felt appropriate to impute 12-month data using multiple imputation for subjects who are prescribed IXT treatment other than overminus or non-overminus refractive correction (e.g. surgery, vision therapy,

patching), an approach which would not be expected to bias the analysis either toward or against a treatment effect of overminus (although any procedure for handling of this issue has some potential for bias). A similar rationale applies to the 18-month off-treatment analyses.

This amendment also provides for the following minor protocol corrections/clarifications:

- Section 2.6.2 was edited to clarify the spectacle prescription for the non-overminus group.
- Section 2.6.1 was edited to clarify that the same is true for the overminus group at 15-months.
- Section 5.4.4 was edited to define the analyses with respect to the added intermittent exotropia symptom survey and the HRQOL questionnaires.
- Section 3.6 was edited to specify what should be done if a masked exam cannot be completed prior to a patient starting non-randomized treatment; and to specify that if the investigator is starting non-randomized treatment, the subject does not return for a stereoacuity retest if stereoacuity is decreased.
- Section 5.2 on the 18-month off-treatment analyses was edited to delete several sections which were redundant with section 5.1 on the 12-month on-treatment analyses. A short paragraph now states that these analyses are repeated at 18 months.
- Sections 5.1.2.1 and 5.3 were edited to indicate that the details of the secondary and additional analyses will be part of a separate statistical analysis plan.

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CHAPTER 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and funded through a cooperative agreement from the National Eye Institute. It is one of a series of randomized trials and observational studies that address management of intermittent exotropia in children.

1.1 Intermittent Exotropia

Intermittent exotropia (IXT) is the most common form of childhood-onset exotropia with an incidence of 32.1 per 100,000 in children under 19 years of age.[1] The onset of IXT is thought to often occur in the first year of life.[2] Among children 1 to 2.5 years of age, IXT has been estimated to occur in 245 children per 100,000.[3] IXT is characterized by an exotropia that is not constant and is mainly present in the distance but may also be present at near.

Treatment for IXT may be either non-surgical or surgical.[4] While surgery is often considered for treatment of IXT, many cases of IXT are treated using non-surgical interventions,[5,6] such as overminus lenses or occlusion.[7]

1.2 Overminus Lens Therapy

Overminus lens therapy involves prescription of additional minus power in the spectacle lenses and the spectacles are worn full-time.

Overminus lens therapy for exodeviations was described as early as 1913 by Landolt.[8] In a survey of US and Canadian pediatric ophthalmologists,[9] 52% reported that they routinely used some form of non-surgical therapy in the management of childhood IXT, with 34% of the 52% using overminus lenses. When the same survey was administered to members of the International Strabismological Association, half of the respondents said they used overminus lenses to treat childhood IXT.[10]

1.3 Possible Mechanisms of Overminus Lens Therapy

The mechanism of overminus lens therapy for IXT is uncertain. It is thought to work by stimulating accommodative convergence, therefore reducing the angle of exodeviation and allowing fusion,[11] or by clearing distance blur (caused by excess compensatory accommodative convergence) and thus allowing fusion.[5] An alternative hypothesis is that fusional convergence often induces convergence accommodation that results in distance blur, but this induced blur is mitigated by minus lenses allowing the better control of the IXT without blur.[12] Regardless of the mechanism, overminus lens therapy may reduce the angle of the exodeviation, or increase the control of the exodeviation (reducing the amount of time the exodeviation is manifest), or both.

1.4 Short-term and Long-term Rationale for Using Overminus Lens Therapy

There appear to be two main reasons for implementing overminus lens treatment in IXT:

- As a temporizing measure to reduce the angle of the exodeviation, or increase the control of the exodeviation, or both, for example in a child considered too young for surgery or vergence training exercises.
- As a long-term strategy, to treat the IXT by improving control of the exodeviation, with eventual weaning of the overminus at a time when the child is well compensated in his or her regular refractive correction.

1.5 Public Health Importance of Proposed Randomized Clinical Trial

Although overminus lens treatment for IXT is widely used in clinical care, there have been no RCTs evaluating its long-term effectiveness. Evaluating the effectiveness of overminus lens treatment for IXT has important public health implications because successful treatment may reduce the proportion of children needing to undergo surgery. Conversely, evidence of poor treatment effectiveness with overminus lens therapy would prevent children from undergoing unnecessary treatment with overminus lenses.

1.6 Previous Studies of Overminus Lens Therapy

Previous studies of overminus lens therapy have been mainly limited to small case series, most with poorly defined methods of prescribing overminus, variable amounts of overminus prescribed, and poorly defined definitions of success (Table 1).

Table 1. Previous studies of overminus lens treatment for IXT

Author, year	Subject population	Method of over-minus determination	Results	Comment
Kennedy 1954[13]	N=103 successfully treated subjects (failures excluded)	Multiple tests of accommodation performed (described in detail by author). "Final lens selected is arrived at in light of all the data yielded by the various tests outlined, and is usually the lowest powered concave lens which produces objective orthophoria." Power may subsequently be changed.	Report only included successful subjects	Success defined as presence of one of the following: "cosmetically straight," "some fusion," or "constant fusion." Treatment duration not reported
Caltrider 1983[14]	N=35 N=10/35 seen 1 year after discontinuing overminus	Prescribed between 2.00D and 4.00D overminus. No other details provided.	46% qualitative improvement in overminus; 7/10 maintained improvement out of overminus	Qualitative improvement defined as neither parents nor physician noticing manifest exodeviation when wearing overminus. Treatment duration from 2 to 156 months

Author, year	Subject population	Method of over-minus determination	Results	Comment
Goodacre 1985[15]	N=34 aged 1 to 6 years	All prescribed 3.00D overminus initially. Amount of minus increased at follow-up if necessary to further improve control (up to a max of 5.00D overminus). No other details provided.	62% "cured"	Cure defined as exophoria near, distance, and far distance when wearing overminus lenses. Treatment duration at least 12 months
Rutstein 1989[16]	N=40 aged 1 to 15 years	Amount of overminus prescribed ranged from 0.50D to 3.75D. No other details provided.	Outcomes not described in terms of overminus success	Main outcome measure was change in refractive error (after wearing overminus). No treatment outcomes reported
Donaldson 1991[17]	N=18 aged 2 to 17 years	"Children of normal retinoscopy were generally ordered 2.00D, 2.50D or 3.00D overminus depending on the ophthalmologist's assessment of expected tolerance."	72% success	Success defined as binocular single vision for all distances & symptoms relieved when wearing overminus lenses. Treatment duration at least 6 months.
Reynolds 1994[11]	N=74 aged 14 months to 13 years	Prescribed 1.00D to 2.50D overminus: the initial amount was "varied according to baseline refractive error and age of subject." No other details provided.	62% success	Success defined as conversion to orthophoria, pure exophoria, or IXT <10pd. Treatment duration at least 3 to 6 months
Kushner 1999[18]	N=74 mean age 4 years	Prescribed overminus spectacles "if seem beneficial in controlling deviation". For myopic refractions: additional 1.00D to 2.00D overminus. For hyperopic refractions: additional minus until final SE between -1.00D and -2.00D. *In addition 4 to 6 prism diopters base in also incorporated in some cases.* If satisfactory control not seen at first follow-up exam, added patching for anti-suppression	19% "improved control" without overminus correction 46% still in overminus 5 years later	Outcomes regarding effectiveness of overminus not clearly reported (study primarily on whether overminus causes myopia). Treatment duration from 6 to 156 months.

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Author, year	Subject population	Method of over-minus determination	Results	Comment
Watts 2005[19]	N=24 aged 2-17 years	Prescribed "maximum tolerated minus": minimum 2.00D to maximum 4.00D depending on ability to read 20/20 and N5 with overminus in place. Hyperopic subjects - Rx reduced by minimum of 2.00D, max 4.00D.	71%	Success defined as improved control (reduction in Newcastle control score) when wearing overminus. Treatment duration 3 months.
Rowe 2009[20]	N=21 aged 1-9 years, Newcastle control score of 3 or worse	Prescribed minimum minus to reduce angle and achieve control of the manifest deviation at near & dist. Started with 1.00D and increased by 0.50D increments until control was achieved. Actual over-minus initially prescribed: median 2.00D; range 1.00D to 3.00D.	24% success (out of overminus)	Success defined as exophoria at near, distance, and far distance, with binocular control at all distances OUT of overminus spectacles at 5 years follow-up. Treatment duration from 6 to 62 months in overminus and from 6 to 39 months out of overminus.
PEDIG 2015	N=58 aged 3-<7 years (n=27 overminus, n=31 non-overminus, Office control score 2 or worse (mean of 3 measures)	RCT: Reduce sphere by 2.50D in overminus group, non-overminus spectacles or no spectacles in non-overminus group	Mean control 2.0 vs 2.8 points favoring overminus. 59% success vs 39% success	Improvement in mean control score from baseline to 8 weeks while on treatment. Success defined as improvement of mean control score 1 point or more at 8 weeks while on treatment.

1.7 Methods of Prescribing Overminus

As illustrated in Table 1 above, the amount of overminus prescribed in previous studies varied from 0.50D to 4.00D, and also differed by the preference for one of 4 philosophical approaches for prescribing overminus:

1. a fixed amount of overminus, regardless of cycloplegic refractive error
2. a fixed amount of overminus over and above cycloplegic refractive error, to achieve a specific amount of accommodative demand
3. a customized approach, tailoring the amount of overminus to a response during a single office examination, either in improved control or improved angle of distance exotropia

4. a customized approach, tailoring the amount of overminus to a response over successive office visits in improved control or improved angle of distance exotropia

1.8 Customized Method of Prescribing Overminus

Although a customized approach to prescribing overminus is sometimes used in clinical practice, there are significant obstacles to incorporating such approach into a rigorous clinical study. The measures used to assess response to overminus are intrinsically variable. Most practitioners use "control" (the proportion of time that the deviation is manifest) to judge response, but although control can be quantified more rigorously in the office using an office control score,[21] a single control score has been found to be highly variable.[22] Adequate representation of control can better be achieved by measuring control at least three times during an office exam and calculating a mean value.[23]

Prior to embarking on the IXT3 pilot study, members of the IXT3 Planning Committee piloted the assessment of control through several steps of increasing or decreasing the overminus lens power to determine a power that better controls the IXT, in a single office examination. We found this method far too time consuming and unworkable for the proposed RCT even when assessing response to each level of overminus with a single measure of control.

In summary, it would be very challenging to develop a protocol that would allow for customized prescribing of overminus using established methods for assessing control.

1.9 Fixed Method of Prescribing Overminus

Whereas some clinicians prescribe a fixed overminus spectacle correction regardless of the cycloplegic refraction (e.g., -1.50D spectacles for a patient with plano and for a patient with +0.50D hyperopia), others prescribe a predetermined amount of overminus by adding the minus power to the cycloplegic refraction e.g., adding -1.50D overminus for all subjects, they would prescribe -1.50D spectacles for plano and -1.00D spectacles for +0.50D hyperopia.

Polling the PEDIG Investigator group at an Investigator meeting (Feb. 7, 2014) revealed that the vast majority (>95%) would prefer a prescribing approach that standardized the amount of induced accommodation achieved by adding a fixed amount of overminus to the cycloplegic refraction. This method reflects the commonly held belief that the treatment mechanism of overminus is related to induced accommodation.

A fixed amount of overminus (-2.50D) was implemented successfully in the recently completed PEDIG IXT3 randomized pilot study and results were encouraging that this dose of overminus appeared effective.

1.10 Determining Dose of Overminus for Current Study

In the IXT2 study (patching versus observation) we found that a large proportion of 3- to <11-year-old children (the target age range for this overminus study) presented with low levels of hyperopia. Nearly all such children were not wearing spectacles because they were able to accommodate well and did not need the hyperopic correction for excellent visual acuity. If we are to include children with hyperopia in a study of overminus lenses, we can only include those with low levels of hyperopia if we want to limit the amount of overminus. Otherwise, we would create untenable situations, such as including a subject with +2.50D hyperopia, prescribing 2.50D overminus, writing a spectacle prescription for 0.00D sphere, and calling this prescription "overminus" treatment.

The consensus of the IXT3 Planning Committee, affirmed by the Investigator Group at the February 2014 Study Group meeting, was that a final spectacle prescription of -1.50D SE should be the lowest level of overminus spectacles prescribed and still be considered "overminus" for a RCT. Doses of overminus greater than 2.50D were of concern to many PEDIG Investigators. For example, overminus of 4.00D was felt to be unreasonable, requiring accommodation of 4.00D at distance fixation and 7.00D for near activities and reading.

A reasonable dose of overminus for the IXT3 pilot study was therefore felt to be -2.50D over the cycloplegic refraction. The dose of -2.50D was successfully implemented in the study, was tolerated well, and appeared to be effective. In an effort to offer a consistent level of overminus treatment for all subjects in IXT3, the study was limited to children with up to +1.00D SE hyperopia, and a standard overminus of 2.50D was prescribed to all subjects. This ensured that the final spectacle prescription of -1.50D SE was the lowest level of overminus spectacles prescribed while maintaining a constant accommodative demand. Given the acceptability and promising results in IXT3 pilot RCT, a dose of -2.50D over the cycloplegic refraction will also be used in the present full RCT. For the analogous reasons described above, hyperopic refractive error in the present full RCT will also be limited to ≤1.00D SE hyperopia.

1.11 Results of the IXT3 Pilot RCT

The IXT3 pilot RCT was designed to evaluate the short-term effectiveness of overminus spectacles in improving control of IXT. 58 children ages 3 to < 7 years old with IXT were randomized to receive either overminus spectacles (-2.50D over cycloplegic refraction) or observation (non-overminus spectacles if needed, or no spectacles) and control was assessed by a masked examiner after 8 weeks of treatment. At 8 weeks, mean distance control was better in the 27 children treated with overminus spectacles than in the 31 children who were observed without overminus treatment (2.0 vs 2.8 points, difference = -0.80 points (95% CI = -1.49 to -0.11 points), P = 0.01 for one-sided test). When defining a treatment response as an improvement in mean distance control score of 1 point or more, 59% of subjects in the overminus group versus 39% of subjects in the observation group were classified as responders (Difference 21%; 95% CI -6% to 45%; P=0.07 for one-sided test). No significant differences were observed between groups when comparing mean near control score or the proportion of subjects with near control improving 1 point or more. Side effect profiles regarding headaches, eyestrain, avoidance of near activities, and blur appeared similar between treatment groups.

Prior to the start of IXT3, criteria were determined for making the decision whether to proceed to a long-term RCT of overminus treatment for IXT. Based on the mean difference in distance control, if the difference in mean favored overminus and P≤0.05, the decision would be to proceed. If the difference in mean favored overminus but P>0.05, the decision to proceed was classified as uncertain. If the difference in mean did not favor overminus, the decision would be to not proceed. Regarding the proportion of subjects with distance control improving 1 point or more, if the response rate in overminus subjects was 20% or more than the response rate in the observation group, the decision would be to proceed with a larger RCT. If that same difference in proportions was 10-19% higher in the over minus group, the decision would be uncertain, and if the response rate was <10% higher in the overminus group, the decision would be to not proceed. Based on the findings of the IXT3 pilot RCT, with a difference in mean distance control of -0.80 points with P=0.01 (favoring overminus) and a difference in response rate of 21%, the decision whether to proceed to a larger scale RCT was to proceed using each set of criteria. We therefore concluded that we should conduct a larger and longer

trial to assess the effectiveness of overminus treatment on the ability to control IXT, both while on treatment and after discontinuing treatment.

1.12 Questions Related to Overminus Lens Therapy

The recently completed IXT3 pilot study addressed the question of whether overminus lens therapy has an initial short-term therapeutic effect for IXT while wearing overminus spectacles. There have been no rigorous studies that address the following important questions related to overminus lens therapy:

- Does overminus lens therapy have a long-term therapeutic effect for IXT while wearing overminus spectacles (over many months or years)?
- Does overminus lens therapy have a long-term therapeutic effect for IXT after overminus spectacles are discontinued?

1.13 Definitions of Treatment Response

Previous studies have differed in their definitions of treatment response, including reduction of the magnitude of exodeviation,[11,14,24] improved control,[20,25] or both combined with good stereoacuity and good cosmesis assessed by parental impression.[24] Some studies report outcomes while the subject is still in overminus lens treatment,[19,25] some post-treatment,[14,20] and for others, treatment status at outcome is unclear.[11,13,24]

Because the initial purpose of the treatment of IXT with overminus spectacles is to better align the eyes for a greater proportion of the time, and single binocular vision with high grade stereoacuity is only associated with good ocular alignment, it would seem reasonable to primarily focus on improved "control" of the distance deviation as the first step in evaluating effectiveness of overminus lens treatment. Due to the variability of single measures of control, we used the recently described "triple control score,"[23] a mean of 3 measures obtained at standardized times during a 20- to 40-minute office examination in the IXT3 pilot RCT, which was easily implementable. Therefore, we will use the "triple control score" as the primary outcome measure in the proposed full RCT.

Treatment effect will be assessed in our study by comparing the treatment group mean control scores at the outcome examination (primary analysis) and by comparing the proportion of subjects with "treatment response" (secondary analysis).

Data simulations were used to estimate the amount of change in control expected from test-retest variability (including short term variability of the condition) and to evaluate the risk of misclassification using various thresholds for defining treatment response. A set of 10,000 stable subjects each with a mean control score (average of 3 measurements) of 2 or worse was simulated using 1) the distribution of baseline distance control scores from subjects 3 to <11 years of age in the IXT2 study who would be eligible for the present study to estimate initial control scores, and 2) actual test-retest data collected on 336 test-retest pairs from 158 IXT subjects at the Mayo Clinic to estimate the probability that a subsequent score would be a certain value (e.g., probability that a control score of five would subsequently test a three). Based on the simulated data, the mean difference in control expected from test-retest variability was estimated at -0.058 points with a standard deviation of 0.926 points. The simulations-estimated 95% limits of agreement of 1.82 points indicated that for a given subject, a 2-point change in the mean control score would be required to have reasonable certainty of exceeding test–retest variability. Using a 2-point threshold, the simulations yielded a misclassification rate for improvement of 2% assuming no real change has occurred.

Nevertheless, defining response as a 2-point change was ultimately not felt to be feasible given that the target population in which overminus lenses are often used includes subjects with control scores as low as 2 points (no exotropia unless dissociated, recovers in > 5 seconds) and that it was felt very unlikely that a large proportion of such subjects could improve to a score of 0 (pure phoria). Consequently, the IXT3 Planning Committee consensus was that a clinically meaningful "response" would be defined as an improvement of at least 1 point on the mean control score. For a 1-point threshold (the secondary outcome measure in IXT3), the simulations yielded a misclassification rate for improved versus not improved of 18% assuming no real change has occurred. Therefore, in IXT3, the control group response rate was estimated to be 18% (rounded to 20%) assuming no real change occurs. As a result, it is acknowledged that the response rate was overestimated in both treatment groups. The same issues exist for the analogous secondary analyses in the current full RCT; hence, the proportion of subjects with both a 1-point and 2-point change are secondary outcomes, and the primary analysis will be based on a group comparison of the continuous measure of control.

1.14 Timing of Outcome Intervention for Current Study

The results of IXT3 suggest that a short-term (8 weeks) treatment with overminus spectacles is effective in improving control while wearing overminus spectacles without inducing significant adverse events. It is therefore reasonable to conduct a larger and longer full-scale RCT to evaluate the long-term on-treatment effectiveness of overminus lenses (e.g., 12 months) and then evaluate the subsequent effectiveness of maintaining control during a weaning period (e.g., 3 months) and after the overminus lens treatment has been discontinued (e.g., 3 months after return to non-overminus spectacles).

1.15 Study Objective

The objectives of this randomized trial comparing overminus lens treatment to non-overminus (spectacles without overminus or spectacles with plano lenses) are to determine:

- The long-term on-treatment effect of overminus treatment on distance IXT control score (primary objective).
- The off-treatment effect of overminus treatment on distance IXT control score, following weaning* and 3 months off treatment (secondary objective).

**Note that weaning was changed to immediate discontinuation of overminus in Protocol Amendment II).*

1.16 Synopsis of Study Design

Major Eligibility Criteria *(see section 2.2 for a complete listing)*

- Ages 3 to < 11 years
- IXT (manifest deviation) meeting all of the following criteria:
  - At distance: IXT or constant XT (mean distance control score of 2 points or more on scale of 1 to 5)
  - At near: IXT, exophoria, or orthophoria (mean near control $\leq$4 points on scale of 1 to 5)
  - Exodeviation $\geq 15\Delta$ at distance by PACT
  - Near deviation does not exceed distance by more than 10Δ by PACT
- No treatment for IXT or amblyopia (other than refractive correction) within the past 4 weeks, including vision therapy, patching, atropine, or other penalization.
- No substantial overminus treatment (spectacles overminused by more than 1.00D SE than the most recent cycloplegic refraction) within the past 6 months
- No prior strabismus, intraocular, or refractive surgery (including Botox injection)

- Refractive error between -6.00D SE and +1.00D SE (inclusive) in the most myopic / least hyperopic eye *(based on a cycloplegic refraction performed within 2 months or at the end of the enrollment exam)*

Sample size and Treatment Groups

Sample size has been estimated to be 384 subjects, randomly assigned (1:1) to the following groups:

- Overminus Group (-2.50D over the cycloplegic refraction)
- Non-overminus Group (non-overminus glasses of full cycloplegic refraction. Except hyperopes (SE) will have full correction of astigmatism with the sphere component adjusted symmetrically so that the SE is plano in the least hyperopic eye; if no astigmatism is present, hyperopes will wear a plano lens in the least hyperopic eye with the sphere of the fellow eye adjusted symmetrically from the cycloplegic refraction.)

Visit / Contact Schedule

All visits/contacts are timed from randomization unless otherwise specified

- Enrollment Visit
- Repeat Enrollment Visit (within 1 month of initial Enrollment, if needed)
- 1-Month Phone call: 3 weeks (3-4 weeks)
- 3-Month Phone call: 3 months (3-4 months)
- 6-Month Office Visit: 6 months ± 1 month
- 9-Month Phone call: 9 months (9-10 months)
- 12-Month On-Treatment Primary Outcome Visit: 12 months ± 1 month
- 13-Month Phone call: 3-4 weeks following 12-month visit
- 15-Month Partial-Treatment* Visit: 15 months ± 1 month
- 16-Month Phone call: 3-4 weeks following 15-month visit
- 18-Month Off-Treatment Primary Outcome Visit: 18 months ± 1 month

*Or Off Treatment Interim Visit for subjects who formally discontinued treatment before the 15-month visit, after Protocol Amendment II.

Testing Procedures

Distance and near control of IXT (3 measurements), cover test, distance and near PACT, and near stereoacuity will be measured by a study-qualified examiner at enrollment, and by a Masked Examiner at all follow-up visits. Distance visual acuity will be measured by a study-qualified examiner at all visits. Health-related quality of life, symptoms of intermittent exotropia, and symptoms that may be associated with overminus spectacle wear will be assessed at enrollment and the 6-month, 12-month and 18-month outcome visits. Cycloplegic refraction will be performed at the end of the enrollment visit (if not performed within prior 2 months) and at the 12-month and 18-month visits.

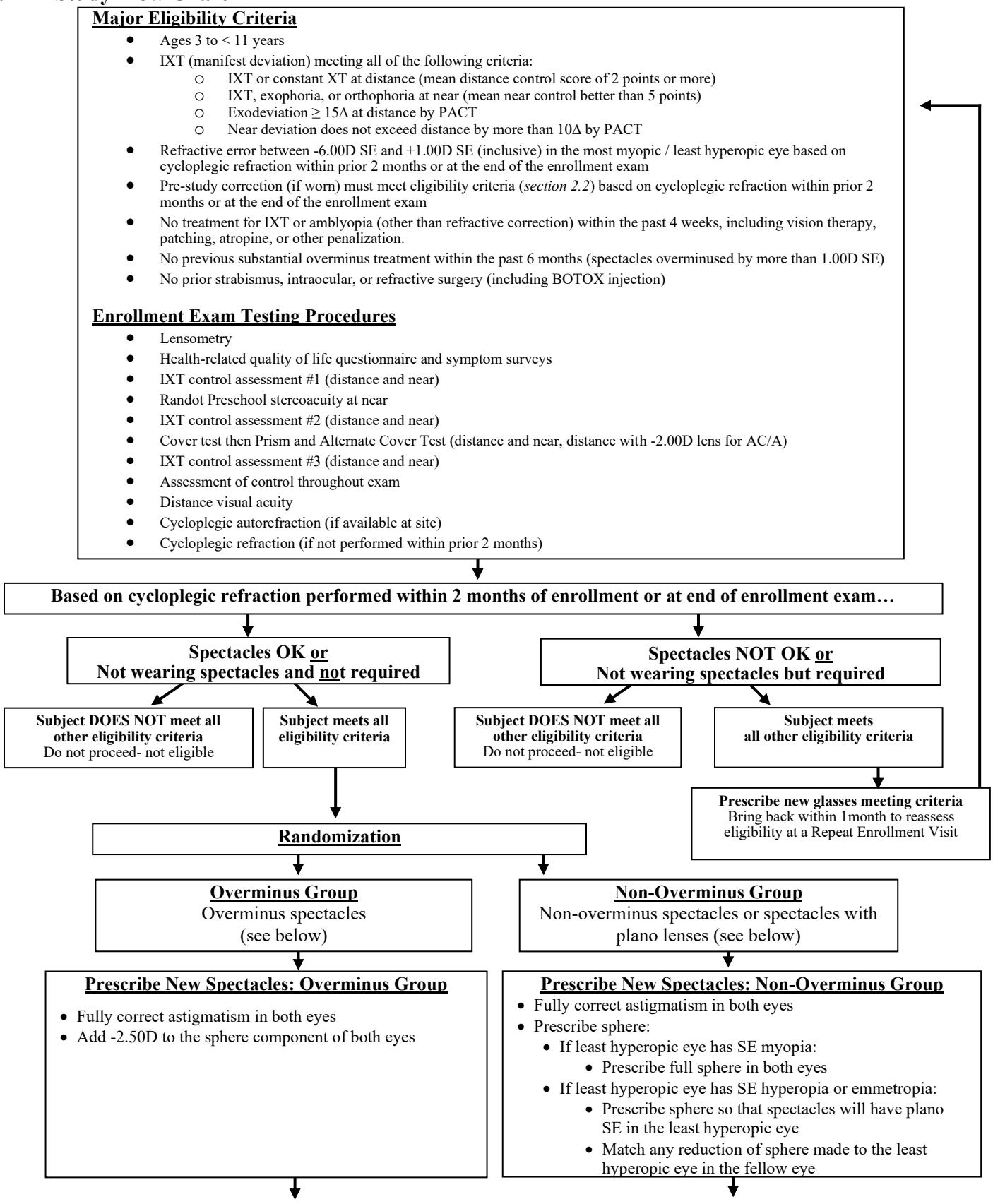
Primary Analysis

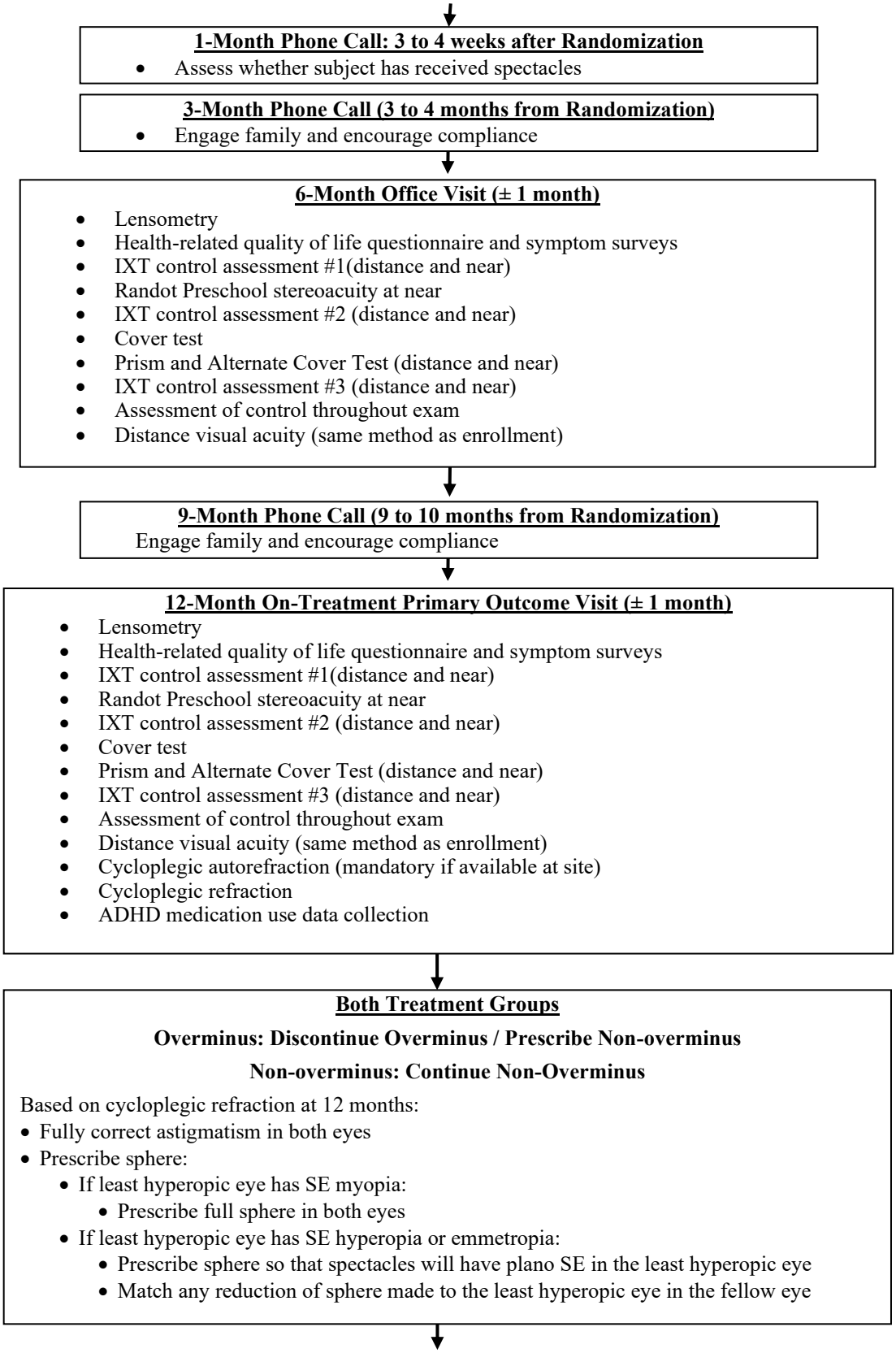
- Treatment group comparison of mean distance control scores (mean of 3 assessments during the exam) at 12 months (on-treatment comparison)

Secondary Analysis

- Treatment group comparison of mean distance control scores (mean of 3 assessments during the exam) at 18 months (off-treatment comparison)

1.17 Study Flow Chart




1-Month Phone Call: 3 to 4 weeks after Randomization
Assess whether subject has received spectacles
3-Month Phone Call (3 to 4 months from Randomization)
Engage family and encourage compliance
6-Month Office Visit (± 1 month)
Lensometry
Health-related quality of life questionnaire and symptom surveys
IXT control assessment #1(distance and near)
Randot Preschool stereoacuity at near
IXT control assessment #2 (distance and near)
Cover test
Prism and Alternate Cover Test (distance and near)
IXT control assessment #3 (distance and near)
Assessment of control throughout exam
Distance visual acuity (same method as enrollment)
9-Month Phone Call (9 to 10 months from Randomization)
Engage family and encourage compliance
12-Month On-Treatment Primary Outcome Visit (± 1 month)
Lensometry
Health-related quality of life questionnaire and symptom surveys
IXT control assessment #1(distance and near)
Randot Preschool stereoacuity at near
IXT control assessment #2 (distance and near)
Cover test
Prism and Alternate Cover Test (distance and near)
IXT control assessment #3 (distance and near)
Assessment of control throughout exam
Distance visual acuity (same method as enrollment)
Cycloplegic autorefraction (mandatory if available at site)
Cycloplegic refraction
ADHD medication use data collection
Both Treatment Groups
Overminus: Discontinue Overminus / Prescribe Non-overminus
Non-overminus: Continue Non-Overminus
Based on cycloplegic refraction at 12 months:
Fully correct astigmatism in both eyes
Prescribe sphere:
If least hyperopic eye has SE myopia:
Prescribe full sphere in both eyes
If least hyperopic eye has SE hyperopia or emmetropia:
Prescribe sphere so that spectacles will have plano SE in the least hyperopic eye
Match any reduction of sphere made to the least hyperopic eye in the fellow eye

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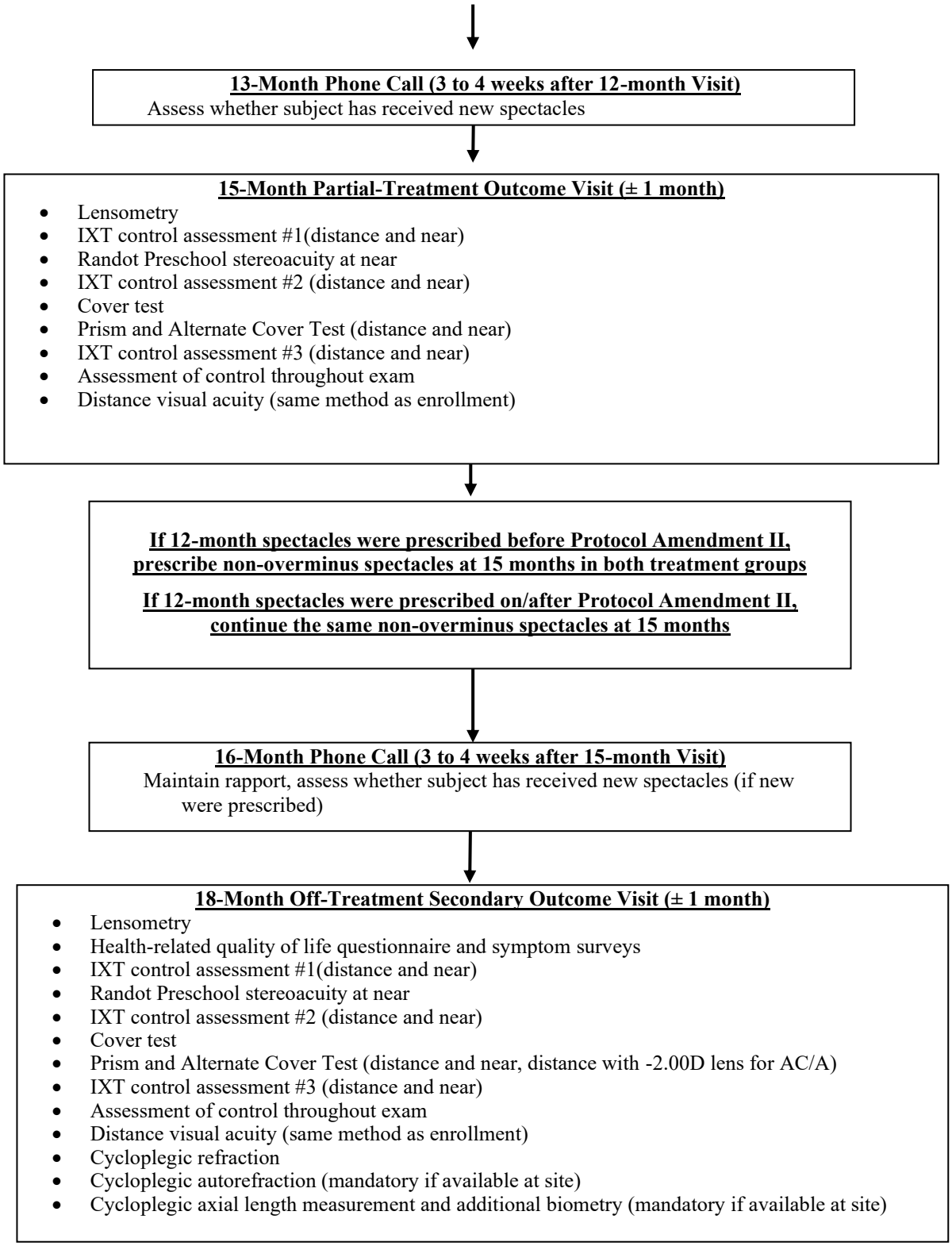
13-Month Phone Call (3 to 4 weeks after 12-month Visit)
Assess whether subject has received new spectacles
15-Month Partial-Treatment Outcome Visit (± 1 month)
Lensometry
IXT control assessment #1(distance and near)
Randot Preschool stereoacuity at near
IXT control assessment #2 (distance and near)
Cover test
Prism and Alternate Cover Test (distance and near)
IXT control assessment #3 (distance and near)
Assessment of control throughout exam
Distance visual acuity (same method as enrollment)
If 12-month spectacles were prescribed before Protocol Amendment II, prescribe non-overminus spectacles at 15 months in both treatment groups
If 12-month spectacles were prescribed on/after Protocol Amendment II, continue the same non-overminus spectacles at 15 months
16-Month Phone Call (3 to 4 weeks after 15-month Visit)
Maintain rapport, assess whether subject has received new spectacles (if new were prescribed)
18-Month Off-Treatment Secondary Outcome Visit (± 1 month)
Lensometry
Health-related quality of life questionnaire and symptom surveys
IXT control assessment #1(distance and near)
Randot Preschool stereoacuity at near
IXT control assessment #2 (distance and near)
Cover test
Prism and Alternate Cover Test (distance and near, distance with -2.00D lens for AC/A)
IXT control assessment #3 (distance and near)
Assessment of control throughout exam
Distance visual acuity (same method as enrollment)
Cycloplegic refraction
Cycloplegic autorefraction (mandatory if available at site)
Cycloplegic axial length measurement and additional biometry (mandatory if available at site)

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CHAPTER 2: ENROLLMENT AND RANDOMIZATION

2.1 Eligibility Assessment and Informed Consent

The randomized trial will include approximately 384 subjects aged 3 to < 11 years with IXT. As the randomization goal approaches, sites will be notified of the end date for recruitment. Subjects whose parents have signed an informed consent form may be entered into the randomized trial up until the end date, which means the expected number for the randomized trial might be exceeded. The maximum number of randomly assigned subjects will be 450.

A child is considered for the study after undergoing a routine eye examination (by a study investigator as part of standard care) that identifies IXT that appears to meet the eligibility criteria. The study will be discussed with the child's parent(s) or guardian(s) (referred to subsequently as parent(s)). Parent(s) who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent must be obtained from the parent prior to performing any study-specific procedures that are not part of routine care.

2.2 Eligibility Criteria

The following criteria must be met for the child to be enrolled in the study:

Inclusion Criteria

- Age 3 years to < 11 years
- Intermittent exotropia (manifest deviation) meeting all of the following criteria:
  - At distance: intermittent exotropia or constant exotropia
    - Mean distance control score of 2 points or more (mean of 3 assessments over the exam)
  - At near: intermittent exotropia, exophoria, or orthophoria
    - Subject cannot have a score of 5 points on all 3 near assessments of control
  - Exodeviation at least 15Δ at distance measured by PACT
  - Near deviation does not exceed distance deviation by more than 10Δ by PACT (convergence insufficiency type IXT excluded)
- Distance visual acuity (any optotype method) in each eye of 0.4 logMAR (20/50) or better if age 3 years and 0.3 logMAR (20/40) or better if 4 years or older.
- Interocular difference of distance visual acuity ≤0.2 logMAR (2 lines on a logMAR chart)
- Refractive error between -6.00D SE and +1.00D SE (inclusive) in the most myopic / least hyperopic eye *based on a cycloplegic refraction performed within the past 2 months or at the end of the enrollment exam*.
- If refractive error *(based on cycloplegic refraction performed within past 2 months or at the end of the enrollment exam)* meets any of the following criteria, then pre-study spectacles are required and must have been worn for at least 1 week prior to enrollment:
  - SE anisometropia ≥1.00D
  - Astigmatism ≥1.50D in either eye
  - SE myopia ≥-1.00D in either eye

  Pre-study refractive correction, if worn, must meet the following criteria relative to the cycloplegic refraction *performed within past 2 months or at the end of the enrollment exam*:
  - SE anisometropia must be corrected within <1.00D of the SE anisometropic difference

    - Astigmatism must be corrected within <1.00D of full magnitude; axis must be within 10 degrees.
    - The SE of the spectacles must not meet the definition of substantial overminus (*see exclusion criteria below*)
- Gestational age ≥ 32 weeks
- Birth weight > 1500 grams
- Parent understands the protocol and is willing to accept randomization to overminus spectacles or non-overminus spectacles
- Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff and Investigator's site staff
- Relocation outside of area of an active PEDIG site within next 18 months is not anticipated

Exclusion Criteria

- Treatment for IXT or amblyopia (other than refractive correction) within the past 4 weeks, including vision therapy, patching, atropine, or other penalization.
- Current contact lens wear
- Substantial deliberate overminus treatment within the past 6 months, defined as spectacles overminused by more than 1.00D SE than the cycloplegic refractive error *(assessed within 2 months or at the end of the enrollment exam)*
- Prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- Abnormality of the cornea, lens, or central retina
- Down syndrome or cerebral palsy
- Severe developmental delay which would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delays or reading and/or learning disabilities are not excluded.
- Any disease known to affect accommodation, vergence, and ocular motility such as multiple sclerosis, Graves orbitopathy, dysautonomia, myasthenia gravis, or current use of atropine for amblyopia
- Anti-seizure medications [e.g., carbamazepine (Tegretol, Carbatrol, Epitol, or Equetro), diazepam (Valium or Diastat), clobazam (Frisium or Onfri), clonazepam (Klonopin), lorazepam (Ativan), ethosuximide (Zarontin), felbamate (Felbatol), lacosamide (VIMPAT), gabapentin (Neurontin), oxcarbazepine (Oxtellar XR or Trileptal), phenobarbital, phenytoin (Dilantin or Phenytek), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), valproate (Depakote), or zonisamide (Zonegran), vigabatrin (Sabril)]

2.3 Historical Information

Historical information elicited will include the following: date of birth, sex, race, ethnicity, cycloplegic refraction, cycloplegic autorefraction (performed within 2 months or at enrollment), prior treatment for IXT, spectacle correction, and use of ADHD and anti-seizure medications.

2.4 Testing at the Enrollment Visit

Initial testing at the enrollment visit should be performed without cycloplegia and with the subject's habitual correction (with spectacles if currently wearing, or without spectacles if not

currently wearing).* Trial frames should NOT be used for testing at the enrollment visit for any reason.

* The exception is a subject wearing spectacles not required by pre-randomization criteria (*see section 2.2*). This subject can be tested with or without these spectacles, provided visual acuity criteria are still met under the condition in which they are evaluated (*see section 2.2*).

There is no specified "waiting" time that needs to occur between measurements, although testing must be performed in the following specified order at the enrollment visit, an exception being that distance visual acuity can be tested either at the start of the visit or at the end of the visit:

1. Spectacle Prescription Verification (Lensometry): Prior to performing the enrollment examination, the subject's pre-randomization spectacle correction (if worn) is to be verified using a lensometer.
2. Health-Related Quality of Life Questionnaire and Symptom Surveys:
    - A brief survey of symptoms that may be associated with overminus such as headaches, eye strain, and problems with spectacle wear will be administered to the parents of the subjects. Parents are asked to respond to the survey questions based on their observations of their child in the past 2 weeks.
    - A brief survey of intermittent exotropia symptoms will be administered to the child.
    - Health-related quality of life (HRQOL) will be assessed using the following two components of the Intermittent Exotropia Questionnaire (IXTQ).[26,27]
        1. Child IXTQ: A child questionnaire for children ages 5 years or older to assess how the child feels about his/her eye condition. Children 4 years and younger at the time of enrollment will not complete the child questionnaire.
        2. Parent IXTQ: A parental questionnaire to assess how the child's eye condition affects the parent (in all children).

STEPS 3 through 9 must be performed in the specified order by the same study-certified examiner (pediatric ophthalmologist, pediatric optometrist, or certified orthoptist) on the same day.

3. Control of the Exodeviation #1:

    Control of exodeviation will be assessed in the habitual correction at distance and near using a standardized IXT control scale (*see below*).[21]
    - Distance (6 meters) – fixing on an accommodative target such as a video or reading optotype letters
    - Near (1/3 meter) – fixing on Lang near-viewing stick or similar accommodative target

    The scale below applies to both distance and near separately.

    Intermittent Exotropia Control Scale
    5 = Constant Exotropia

4 = Exotropia > 50% of the 30-second period before dissociation
3 = Exotropia < 50% of the 30-second period before dissociation
2 = No exotropia unless dissociated, recovers in >5 seconds
1 = No exotropia unless dissociated, recovers in 1-5 seconds
0 = No exotropia unless dissociated, recovers in <1 second (phoria)
Not applicable = No exodeviation present

Directions:

Step1: Assessment before any dissociation: Levels 5 to 3 are assessed during a 30-second period of observation; first at distance fixation and then at near fixation for another 30-second period. Both distance and near are assessed before any dissociation (i.e., before step 2, when assessing control scores of 0, 1 and 2). If the subject is spontaneously tropic (score 3, 4 or 5) at a specified test distance, then step 2 (assessment after standard dissociation) is skipped at that specific test distance.

Step 2: Assessment with standardized dissociation: If no exotropia is observed during step 1 (i.e., the 30-second period of observation at the specified test distance), levels 2 to 0 are then assessed as the worst of 3 rapidly successive trials of dissociation:

1. An occluder is placed over the right eye for 10 seconds and then removed, measuring the length of time it takes for fusion to become re-established.
2. The left eye is then occluded for a 10-second period (second assessment under dissociation) and the time to re-establish fusion is similarly measured.
3. A third assessment under dissociation is performed, covering the eye (for a 10-second period) that required the longest time to re-fuse.

The worst level of control observed following the three 10-second periods of occlusion should be recorded. Since the level under dissociation is recorded as the worst of the three assessments, if a score of 2 (>5 seconds recovery) is noted on the first or second dissociation, then subsequent dissociation(s) are not needed.

If the patient has a micro-esotropia by cover test but an exodeviation by PACT, the scale applies to the exodeviation.

4. Stereoacuity Testing: Stereoacuity will be assessed with habitual correction (if any) using the Randot Preschool stereotest at near (performed at 40 cm). A specific level of stereoacuity is not required for eligibility.
5. Control of the Exodeviation #2 (repeat) (*see item #3*).
6. Cover Test
   - Assessed in primary position at distance (6 meters) and near (1/3 meters) using procedures outlined in the *IXT Testing Procedures Manual*
7. PACT Testing & AC/A Determination:
   - PACT will be assessed in primary gaze and without cycloplegia as follows and using procedures outlined in the IXT Testing Procedures Manual.
   - At distance (6 meters) and near (1/3 meter) in habitual correction
   - AC/A assessment at distance (6 meters) measuring the PACT with the subject wearing -2.00D lenses over his/her habitual correction. The AC/A ratio is calculated by taking the difference between the distance PACT measurements with and without -2.00D lenses and dividing the difference by 2.
8. Control of the Exodeviation #3 (repeat) (*see item #3*)

9. Assessment of Deviation Throughout Exam
    - The nature of the exodeviation will be classified at distance and near as either constant, intermittent, phoric, or no deviation based on observations of the examiner assessing control during the entire examination period from the first assessment of control through the last assessment of control. The nature of the deviation will be recorded as:
        - Constant if a manifest tropia is present 100% of the time during the examination, including during all 3 control tests (score of 5 for each test)
        - Intermittent if a manifest tropia is present (including after dissociation) but not 100% of the time during the entire exam.
        - Phoric if a tropia is not observed at any time but a phoria is present.
        - No deviation if no deviation is present at any time.
    - If the child appears to have a constant tropia but shows excellent stereoacuity that may be inconsistent with the diagnosis of constant tropia, the examiner should look over the child's polarized glasses to determine whether the child is indeed constantly tropic (by direct observation with a cover test).
10. Distance Visual Acuity Testing: Monocular distance visual acuity testing with the habitual correction and without cycloplegia will be measured using the investigators usual testing procedure.
    - Visual acuity testing method must use optotypes.
    - Visual acuity must be tested using the same testing procedure throughout the entire study.
    - Visual acuity will be recorded as Snellen equivalents in logMAR increments.
    - Visual acuity may be tested at the start of the exam or at the end of the exam (not between steps #3 and #9).
11. Cycloplegic Autorefraction (if available at site):
    - If an autorefractor is available at the site, refractive error must be measured with the autorefractor following cycloplegia with 1% cyclopentolate (*see cycloplegic refraction below*). These measures will be used to determine myopic progression in both groups, but will not be used to assess eligibility or to prescribe spectacle correction during the study. Recorded values will be based on a single measurement by the instrument (which may be a mean of several individual measures, depending on system). The autorefraction should be done on the same day as the cycloplegic refraction, which may be done within 2 months of enrollment.
12. Cycloplegic Refraction:
    - A cycloplegic refraction will be performed at the end of the enrollment visit if not done within 2 months of enrollment.
    - The cycloplegic refraction used to assess eligibility must be/have been performed 30 to 45 minutes following at least one application of cyclopentolate 1% per investigator's usual dosage and timing routine.
        - The cycloplegic refraction is based on cycloplegic retinoscopy, which may be done with glasses off or as an over-refraction in front of the current spectacles. Subjective refraction is allowed.
        - When an over-refraction of current eye glasses is performed, the reported cycloplegic refraction will be the sum of the current spectacle power and the over-refraction.
13. Additional Clinical Testing:

- Ocular examination as per investigator's clinical routine to rule out ocular abnormality or lens opacity (if not performed within 7 months)

All testing must be performed within 7 days before randomization except where otherwise noted above.

2.5 Confirmation of Eligibility / Timing of Randomization

All testing to assess eligibility for randomization must be performed without cycloplegia and with the subject's current correction (with spectacles if currently wearing or without spectacles if not currently wearing).

Eligibility criteria relating to refractive error and spectacle correction are based upon the cycloplegic refraction done within 2 months of enrollment or at the end of the enrollment exam (for subjects without a prior cycloplegic refraction performed within 2 months of enrollment).

- If all eligibility criteria are met (including appropriate pre-study refractive correction, if required—*see section 2.2*), the subject should be randomized on the day of enrollment testing (or up to 7 days later).
- If all eligibility criteria are met *other than* the subject needing to be prescribed new pre-study refractive correction or needing a change in pre-study refractive correction (*section 2.2*):
    - Prescribe new spectacles paid for by the study
    - Have the subject return for a repeat enrollment exam (paid for by the study) within 1 month and after wearing the new pre-study spectacles for at least 1 week. All enrollment testing except cycloplegic refraction must be repeated.
        - If the subject meets all eligibility criteria at the repeat enrollment exam, he/she will be eligible for randomization at that time (or up to 7 days later).
        - If the subject fails any eligibility criteria at the repeat enrollment exam, the patient is not eligible for randomization and will end study participation.

2.6 Randomization

Randomization will occur within 7 days after confirming that the subject meets the eligibility criteria.

Subjects entering the study will be randomly assigned with equal probability to one of the following groups:

- Overminus Group
- Non-overminus Group

The Jaeb Center will construct a separate Master Randomization List using a permuted block design stratified by site and baseline distance control. A subject is officially enrolled in the randomized trial when the website randomization process is completed.

Subjects and parents will be masked to the treatment group assignment.

2.6.1 Treatment for Overminus Group

NOTE: Details of spectacles to be prescribed will be automatically calculated by the study website.

No IXT treatment other than the study spectacles specified below can be prescribed at any time during the study <u>unless the subject meets deterioration criteria</u> described in *section 3.7.*

<u>Enrollment Visit</u>

- Subjects randomly assigned to the overminus group will be prescribed spectacles based on a cycloplegic refraction as follows:
  - Fully correct the astigmatism in both eyes (if present)
  - Add -2.50D to the sphere component of the cycloplegic refraction for both eyes
- Overminus spectacles are prescribed to be worn all waking hours through the 12-month outcome visit.

<u>12-Month Visit*</u>

- At the 12-month outcome visit, overminus treatment will be discontinued and new non-overminus spectacles will be prescribed based on the 12-month cycloplegic refraction as follows*:
  - If the cycloplegic refraction is spherical and plano or any amount of hyperopia in both eyes (with no astigmatism and no anisometropia), subjects will wear spectacles with plano lenses in both eyes to maintain masking.
  - Otherwise, fully correct astigmatism in both eyes and prescribe sphere as follows:
    - If least hyperopic eye has SE myopia:
      - Prescribe the full sphere in both eyes
    - If least hyperopic eye has SE hyperopia or emmetropia:
      - Prescribe sphere so that spectacles will have plano SE in the least hyperopic eye
      - Match any reduction of sphere made to the least hyperopic eye in the fellow eye
  - Subjects will wear the new prescription all waking hours until the 18-month visit.

** Unless the subject has already met deterioration criteria confirmed by masked examiner as described in section 3.7 in which case spectacles are prescribed at investigator discretion.*

<u>15-Month Visit*</u>

- If the 12-month spectacles for a subject were issued **before** Protocol Amendment II and therefore contain partial-strength overminus (-1.25D), the spectacles should be changed to non-overminus spectacles at the 15-month to discontinue the overminus (see 12-month prescribing above).
- If the 12-month spectacles for a subject were issued **on/after** Protocol Amendment II and therefore are already non-overminus spectacles, the non-overminus spectacles should be continued at the 15-month visit.

** Unless the subject has already met deterioration criteria confirmed by masked examiner as described in section 3.7. in which case spectacles are prescribed at investigator discretion.*

2.6.2 Treatment for Non-Overminus Group

NOTE: Details of spectacles to be prescribed will be automatically calculated by the study website.

No IXT treatment other than the study spectacles specified below can be prescribed at any time during the study unless the subject meets deterioration criteria described in *section 3.7.*

Enrollment Visit

- Subjects in the non-overminus group will be prescribed spectacles based on the cycloplegic refraction as follows:
    - If the cycloplegic refraction is spherical and between plano sphere and +1.00D sphere in both eyes (with no astigmatism and no anisometropia), subjects will wear spectacles with plano lenses in both eyes to maintain masking.
    - Otherwise, fully correct the astigmatism and prescribe sphere as follows:
        - If least hyperopic eye has SE myopia:
            - Prescribe the full sphere in both eyes
        - If least hyperopic eye has SE hyperopia or emmetropia:
            - Prescribe sphere so that spectacles will have plano SE in the least hyperopic eye
            - Match any reduction of sphere made to the least hyperopic eye in the fellow eye
- Subjects will wear the new prescription all waking hours until the 12-month visit.

12-Month Visit*

- Spectacles will be updated at the 12- -month visit using the same prescribing guidelines at enrollment (see above) but using the 12-month cycloplegic refraction, unless the subject has already met deterioration criteria confirmed by masked examiner as described in *section 3.7* in which case spectacles are prescribed at investigator discretion.
- To maintain masking, lenses will be replaced even if there is no change in the cycloplegic refraction.

** Unless the subject has already met deterioration criteria confirmed by masked examiner as described in section 3.7 in which case spectacles are prescribed at investigator discretion.*

15-Month Visit*

- If the 12-month spectacles for a subject were issued **before** Protocol Amendment II, the non-overminus lenses should be replaced at the 15-month visit to maintain masking of treatment groups (see 12-month prescribing above).
- If the 12-month spectacles for a subject were issued **on/after** Protocol Amendment II and therefore are already non-overminus spectacles, the non-overminus spectacles should be continued at the 15-month visit.) There is no longer a reason to change the

glasses to maintain masking, because both treatment groups are already wearing non-overminus glasses.

**Unless the subject has already met deterioration criteria confirmed by masked examiner as described in section 3.7 in which case spectacles are prescribed at investigator discretion.*

CHAPTER 3: FOLLOW-UP AND MANAGEMENT

3.1 Follow-up Schedule

The follow-up schedule is timed from randomization as follows:

- 1-Month Phone call: 3 weeks (3-4 weeks)
- 3-Month Phone call: 3 months (3-4 months)
- 6-Month Office Visit: 6 months ± 1 month
- 9-Month Phone call: 9 months (9-10 months)
- 12-Month On-Treatment Primary Outcome Visit: 12 months ± 1 month
- 13-Month Phone call: 3-4 weeks following 12-month visit)
- 15-Month Off-Treatment Interim Visit: 15 months ± 1 month
- 16-Month Phone call: 3-4 weeks following 15-month visit)
- 18-Month Off-Treatment Primary Outcome Visit: 18 months ± 1 month

Additional visits may be scheduled at investigator discretion.

Subjects with a drop (worsening) of 2 or more octaves from baseline in near stereoacuity during follow-up (*see section 3.7*), confirmed by a retest on the same day, will need to return for an additional retest on a subsequent day.

3.2 Telephone Calls

At each time during the study when subjects in both groups receive new study spectacles, the site will contact parents to determine whether the study spectacles (overminus spectacles/non-overminus spectacles/plano spectacles) have been dispensed/received. These calls will occur 3 weeks following the enrollment, 12-month, and 15-month visits as defined above.

The site will record the date that the new spectacles were received or document that they have not been received as of the call date. Parents will be reminded to have their children wear the spectacles all waking hours.

Additional protocol-specified calls to engage the subject and encourage spectacle compliance will be made from the investigator's site at 3 months and 9 months following randomization as defined above.

Additional calls may be made as needed as outlined in *section 4.1*.

3.3 Masking of Treatment Group

Subjects will be masked to treatment group throughout the study. Subjects who do not have refractive error that requires correction (*see sections 2.6.1 and 2.6.2*) will be prescribed plano lenses if randomized to the non-overminus group.

Key outcome testing at each follow-up visit (*see section 3.3.1*) will be performed by an examiner masked to treatment group. Although the examiner will see the subject's spectacles during test, the presumption is that treatment group is unlikely to be discerned because 1) all subjects will be wearing spectacles and 2) because both treatment groups will have a range of prescriptions depending on subjects' underlying refractive error in addition to whether an overminus component is included. The Masked Examiner must be a pediatric ophthalmologist,

pediatric optometrist, or certified orthoptist. The Masked Examiner should preferably be someone *other than* the investigator.

If necessary at rare sites, the Masked Examiner may be the investigator if the investigator remains masked to the randomized treatment. At such sites, for prescription of spectacles throughout the study, the investigator should sign two prescriptions (one overminus prescription and one non-overminus prescription), after which an unmasked coordinator would provide the parent with the appropriate prescription according to the subject's treatment group.

The investigator will be unmasked to treatment group except at rare sites in which he/she must serve as the masked examiner. The investigator should not discuss a subject's treatment group with the subject or his/her parents.

3.3.1 Masked Examiner Testing

A masked examiner will assess the following at the 6-month, 12-month, 15-month, and 18-month visits regardless of whether or not the subject has already met deterioration criteria confirmed by masked examiner as described in *section 3.7* at a previous visit:

- Control assessment #1
- Stereoacuity
- Control assessment #2
- Cover test
- PACT
- Control assessment #3
- Assessment of deviation throughout the exam

The Masked Examiner must not verify the spectacles using lensometry, discuss compliance of spectacle wear with the subject or parents, or administer the symptom survey. The Masked Examiner should not review the subject's medical record prior to the exam.

3.4 Outcome Visit Testing Procedures

If deterioration has NOT been confirmed by masked exam at a previous visit, subjects should be tested in study specific spectacles (i.e., overminus spectacles or non-overminus spectacles including plano spectacles). If deterioration has been confirmed by masked exam at a previous visit, subjects will be tested in their current refractive correction.

Someone *other than* the Masked Examiner will ensure that the subject is wearing the appropriate spectacles (as described above) prior to the masked exam.

Subjects not bringing their spectacles to the outcome visit (or who have had their spectacles discontinued for any reason) will be tested in trial frames. Subjects who have had their spectacles discontinued (not likely to occur) should be tested in plano trial frames. To avoid potential unmasking, the trial lenses must have wire frames (not red or black indicating minus or plus power). Care should be taken to cover any power-indicating markings with tape to ensure that masking is maintained.

The following procedures should be performed by the appropriate examiner (*see below*) and in order where specified:

The following procedures are tested first by someone *other than* the Masked Examiner:

1. Spectacle Prescription Verification (Lensometry): Prior to performing the outcome examination, the subject's spectacle correction will be verified using a lensometer (including plano lenses).
    - Spectacles should meet the following tolerances:
        - Sphere within 0.50D of prescribed
        - Cylinder within 0.50D of prescribed
        - Axis within 10 degrees of prescribed
    - If spectacles do not meet these tolerances, the subject should be tested with trial frames with the intended prescription in place.
2. Compliance Assessment: Compliance with spectacle wear since receiving the spectacles will be assessed based on discussion with the parents and using the following scale:
    - Excellent (76% to 100%)
    - Good (51% to 75%)
    - Fair (26% to 50%)
    - Poor (≤ 25%)
3. Health-Related Quality of Life Questionnaire and Symptom Surveys (6-month, 12-month, and 18-month visits only): The parent and child will complete the same questionnaire and symptom surveys as described at the time of enrollment.

After the above assessments, the following procedures must be performed in the specified order by the Masked Examiner. All procedures should be performed with the subject wearing his/her current study spectacles (or trial frames if study spectacles were not brought to the visit) and without cycloplegia:

Although tests #4 through #10 must be performed in the specified order, there is no specified 'waiting' time that needs to occur between measurements.

4. Control of the Exodeviation #1 **(Masked):** A Masked Examiner will assess control of exodeviation at distance and near fixation using the intermittent exotropia control scale.[28-30]
5. Stereoacuity Testing **(Masked):** Stereoacuity will be assessed using the Randot Preschool stereotest at 40 cm. If the subject has no measurable stereo, this finding will be recorded as "nil".

If stereoacuity has decreased by 2 octaves or more (*see Table 2 below*) from baseline:

- Stereoacuity must be retested on the same day by the masked examiner. Retesting can be performed any time after the final assessment of control (Step 10) but prior to any cycloplegia.
    - If the stereoacuity is still reduced 2 octaves or more from baseline on the same-day retest, the subject must be brought back for a retest of stereoacuity on a different day (*see section 3.5*).

Table 2: Preschool Randot Stereotest

Baseline stereoacuity, in arcsec	Level needed at follow-up visit to require retest, in arcsec
40”	200”, 400”, 800”, nil
60”	400”, 800”, nil
100”	400”, 800”, nil
200”	800”, nil
400”	Nil
800”	Nil
Nil	Not applicable

6. Control of the Exodeviation #2 (repeat) (see item #4) **(Masked)**
7. Cover Test **(Masked):** Assessed in primary position at distance (6 meters) and near (1/3 meter) as outlined in the IXT Testing Procedures Manual.
8. PACT Testing **(Masked):** A Masked Examiner will assess:
    - PACT in primary position at distance (6 meters) and near (1/3 meter) as outlined in the IXT Testing Procedures Manual.
    - AC/A ratio (18-month visit only) at distance (6 meters) measuring the PACT with the subject wearing -2.00D lenses over his/her habitual correction. The AC/A ratio is calculated by taking the difference between the distance PACT measurements with and without -2.00D lenses and dividing the difference by 2.
9. Control of the Exodeviation #3 (repeat) (see item #4) **(Masked*)***
10. Assessment of Deviation Throughout Exam **(Masked)**

The following procedures should be performed by either the Masked Examiner or another study-certified examiner:

11. Distance Visual Acuity Testing: Monocular distance visual acuity testing with the habitual correction and without cycloplegia will be measured using the same testing procedure as used for enrollment. Visual acuity may be tested at the start of the exam or before the cycloplegic refraction.
12. Cycloplegic Autorefraction (12-month and 18-month visits only, mandatory if autorefractor is available at the site)
    - Refractive error must be measured with the same autorefractor used at enrollment following cycloplegia with 1% cyclopentolate (*see cycloplegic refraction below*).
    - If cycloplegic autorefraction was completed at enrollment, then it must be measured with the same autorefractor used at enrollment.
    - Regardless of whether cycloplegic autorefraction was completed at enrollment, it is mandatory to measure cycloplegic autorefraction if an autorefractor is available at the site.
    - Recorded values will be based on a single measurement by the instrument (which may be a mean of several individual measures depending on system)
13. Cycloplegic Axial Length Measurement and Additional Biometry (18-month visit only) (see manual of procedures).

- Axial length
- Flat corneal radius
- Anterior Chamber depth
- Lens thickness, if available

14. Cycloplegic Refraction (12-month and 18-month visits)

- A cycloplegic refraction will be performed at the 12-month and 18-month visits. The cycloplegic refraction will be performed regardless of whether a cycloplegic autorefraction is performed.
- Cycloplegic refraction is performed 30 to 45 minutes following at least one application of cyclopentolate 1% per investigator's usual dosage and timing routine.
- The cycloplegic refraction is based on cycloplegic retinoscopy, which may be done with glasses off or as an over-refraction in front of the current spectacles. Subjective refraction is allowed.
- When an over-refraction of current eye glasses is performed, the reported cycloplegic refraction will be the sum of the current spectacle power and the over-refraction.

15. ADHD and Seizure Medication Use Data Collection (12-month visit only)

- At the 12-month visit, data regarding any ADHD and seizure medication use in the past 12 months will be collected.

3.5 Repeat Stereoacuity Testing on a Subsequent Day

At any follow-up visit (including the 18-month outcome visit), subjects whose near stereoacuity by the Randot Preschool Stereoacuity test is worse by 2 octaves or more from baseline on both the initial test and the same-day retest by a Masked Examiner must return for a retest of stereoacuity by a masked examiner on a subsequent day. This return visit must be within 1 month of the follow-up visit (including the 18-month outcome visit).

- This return visit must also be after the child has received his/her new glasses prescribed at the follow-up visit (applies only to the 12-month and 15-month visits).
- A Masked Examiner must test the stereoacuity at this repeat visit. If stereoacuity is still reduced 2 octaves or more from baseline, stereoacuity is retested after a short rest period.
    - If the stereoacuity has worsened by 2 octaves or more from baseline (confirmed by a retest), the investigator may initiate non-randomized treatment for IXT at his/her discretion (*see section 3.8)*
    - If stereoacuity has not worsened by 2 octaves or more from baseline, the subject will continue the randomized treatment unless the subject has already met deterioration criteria at a previous visit confirmed by masked examiner as described in *section 3.7* in which case spectacles are prescribed at investigator discretion.
- No testing other than stereoacuity testing is required.

3.6 Additional Visits

Investigators may schedule additional visits at their own discretion.

If the investigator plans to initiate non-randomized treatment for IXT at an additional visit, a masked examination (following all testing procedures in *section 3.4* except for the cycloplegic

refraction / autorefraction) must be performed prior to initiating the new treatment. If a masked examiner is unavailable, data from an unmasked exam should be entered on the website, noting that the examiner was unmasked. If the investigator is starting non-randomized treatment, the subject does not return for a stereoacuity retest if stereoacuity is decreased (section 3.7).

3.7 Deterioration Criteria

Subjects who meet either of the following at any visit will be considered to have met deterioration criteria.

- Motor deterioration: Control of the exodeviation measures 5 (constant exotropia) on all three assessments at distance and near. The exodeviation does not need to be constant throughout the entire exam provided that it is constant during all three control testings.
- Stereoacuity deterioration: Drop in near stereoacuity of at least 2 octaves (*as defined in section 3.4*) (at least 0.6 log arcsec) from enrollment stereoacuity, or to nil, confirmed by a retest by a Masked Examiner on a subsequent day (*section 3.5*). Note: subjects with nil stereoacuity at enrollment will not be able to deteriorate with respect to a drop in near stereoacuity.

Subjects who meet deterioration criteria may have non-randomized treatment for IXT started at investigator discretion. Whether or not a subject starts non-randomized treatment for IXT during the study, all subjects will still be followed at regular study visit intervals through the end of the study.

3.8 Initiating Non-Randomized Treatment for IXT

Non-randomized treatment for IXT is not permitted during the study unless the subject has met deterioration criteria (*see section 3.7*). If neither deterioration criterion is met but the subject is experiencing overwhelming social concerns or significant symptoms associated specifically with the exodeviation, the investigator must call the protocol chair to discuss the case and obtain approval for an exception prior to initiating non-randomized treatment for IXT.

Non-randomized treatment for IXT refers to any treatment other than that which the subject was randomized to. It includes but is not limited to:

- Surgery
- Occlusion
- Vergence exercises
- Overminus spectacles (in non-overminus group)
- Cycloplegia
- Formal discontinuation of overminus spectacles (in overminus group) – *note that subject non-compliance with overminus spectacles is not considered formal discontinuation.*

If the investigator plans to initiate non-randomized treatment for IXT at an additional visit rather than a protocol-specified visit, a masked examination must be performed prior to initiating the new treatment (section 3.6).

Subjects who have started non-randomized treatment for IXT during the study will still be followed at regular study visit intervals through the end of the study.

3.9 Treatment of Amblyopia

Given the exclusion of subjects with amblyopia, the rate of developing amblyopia during the study is expected to be low. Nevertheless, if amblyopia develops during the study, the investigator may initiate amblyopia treatment, however initiating atropine, other cycloplegic drops, or levodopa is not allowed.

3.10 Management of Refractive Error

Management of refractive error will follow study guidelines (*see sections 2.6.1 and 2.6.2*) for the duration of the study. A cycloplegic refraction will be performed for all subjects at the 12-month visit and the 18-month visit. These data are used to adjust the glasses at 12-,15- and 18-month visits.

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS

4.1 Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent's contact information. The Jaeb Center will contact the parents of the subjects only when necessary. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the subject and/or family and to help coordinate scheduling of the outcome examinations.

4.2 Subject Withdrawals

Parents may withdraw their child from the study at any time. This is expected to be a very infrequent occurrence in view of the study design's similarity to routine clinical practice. If the parents indicate that they want to withdraw their child from the study, the investigator personally should attempt to speak with them to determine the reason. If their interest is in transferring the child's care to another eye care provider, every effort should be made to comply with this and at the same time try to keep the subject in the study under the new provider's care.

4.3 Risks

There are no risks involved in this study that would not be part of usual care when treating with either overminus or non-overminus lenses.

4.3.1 Risks of Examination Procedures

The procedures in this study are part of daily eye care practice in the United States and Canada and pose no known risks.

4.3.2 Risk of Overminus Lens Therapy

The risks involved in the study are identical to those for a child treated with overminus lens therapy who is not participating in the study.

Some subjects treated with overminus lenses may experience eye strain when wearing the spectacles; the eye strain typically dissipates with removal of the spectacles.

Among previous retrospective reports, some have indicated that there may be an increased rate of myopia development when accommodation is stimulated,[11,18,31] whereas others have reported no increase in myopia following overminus lens therapy. However, unpublished data from the current ongoing randomized trial suggests that myopic progression over one year is greater in subjects treated with overminus lenses vs. those treated with non-overminus lenses, and that myopic progression was most often observed in overminus group subjects who had spherical equivalent myopia of -0.50 D or greater at baseline (PEDIG unpublished, 2019).

4.3.3 Risk Assessment

It is the investigators' opinion that the protocol's level of risk falls under DHHS 46.404, which is research not involving greater than minimal risk.

4.4 Reporting of Adverse Events

Although no adverse events are anticipated as a result of overminus therapy or non-overminus spectacle wear, any new cases of amblyopia, constant esotropia, or constant exotropia at distance and near will be reported. No surgical procedures are part of the protocol and no treatments are

being prescribed that are not part of usual care. Investigators will abide by local IRB reporting requirements.

4.5 Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the pre-planned completion of enrollment and follow-up for all subjects.

4.6 Travel Reimbursement

The parent of each subject will be compensated $50 for completion of each of the following visits: the enrollment, repeated enrollment (if required), 6-, 12-, 15-, and 18-month visits, and any additional visits (i.e. if required prior to starting alternative treatment or required to retest stereoacuity). If there are extenuating circumstances, and the subject is unable to complete a study visit without additional funds due to travel costs, additional funds may be provided.

4.7 Study Costs

The study will pay for visits specific to the research study, but will not pay for usual care visits that would occur whether or not the subject was in the study. The cost of usual care visits will be the responsibility of the subject or his/her insurance company.

Study spectacles (frames and lenses) will be provided by the study at enrollment (if necessary, as described in *section 2.5*), at randomization, 12-, 15-, and 18-month visits, at no cost to the subject.

The study will not pay for bifocal lenses or photochromic lenses.

4.8 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic CRFs, which will be considered the source data.

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

A risk-based monitoring approach will be followed, consistent with the FDA “Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring” (August 2013).

CHAPTER 5: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized without knowledge of study data. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan, which will supersede these sections when it is finalized.

5.1 Primary Objective: Efficacy on Overminus Treatment (12 Months)

The primary objective is to determine the efficacy of overminus lenses after 12 months of treatment.

5.1.1 Primary Analysis - Mean Distance Control at 12-Months (On-Treatment)

The primary analysis will be a two-sided comparison of mean 12-month control of the distance exodeviation (average of 3 measurements) between treatment groups using an analysis of covariance (ANCOVA) model, which adjusts for baseline distance control, distance PACT, age, refractive error, and use of ADHD medication, to address potential residual confounding.

The treatment group difference (overminus – non-overminus) and a 95% confidence interval will be calculated.

The 12-month distance control score for analysis for each subject is the mean of the 3 control assessments completed at the visit. When the protocol-specified three measures of control are not performed at the outcome exam, the mean of two tests will be used for analysis if only 2 distance control tests are completed; the single distance control score will be used for analysis if only 1 testing is completed.

The primary analysis will follow a modified intention-to-treat principle, with all subjects analyzed according to their randomized treatment group and with the following stipulations:

- Subjects who are treatment crossovers (non-overminus group subjects who are prescribed overminus; overminus group subjects who have overminus spectacles formally discontinued) will have their observed 12-month data analyzed provided they complete at least one distance control testing at the 12-month outcome exam; otherwise their average distance control score will be imputed using multiple imputation.
- Subjects who are prescribed IXT treatment *other than overminus or non-overminus refractive correction* (e.g. surgery, vision therapy, patching) will have their average distance control score imputed using multiple imputation, regardless of whether any control testing is completed at the 12-month visit.
- Subjects who miss the 12-month visit or who do not complete any control testing at the 12-month visit will also have their average distance control score imputed using multiple imputation.[32]

The multiple imputation will be performed using Monte Carlo Markov Chain (MCMC) modeling that includes data from baseline and follow up visits *(for subjects who are prescribed IXT treatment other than overminus or non-overminus refractive correction, only data from visits up to and including the visit at which treatment was prescribed will be used).*

The primary analysis will include subjects who enter the randomized trial but are later found to be ineligible.

5.1.1.1 **Alternatives to the Primary Analysis**

The following analyses will be performed as alternatives to the primary analysis:

Alternative Analysis #1:

- All subjects who complete 1 or more distance control testing at the 12-month visit, including treatment crossovers and subjects who are prescribed IXT treatment other than overminus or non-overminus refractive correction, will have their observed 12-month data analyzed.
- Subjects who miss the 12-month visit entirely or who do not complete any control testing at the 12-month visit will be excluded from the analysis.

Alternative Analysis #2:

- Subjects who are prescribed IXT treatment other than overminus or non-overminus refractive correction for any reason at any time before the 12-month visit will have the average distance control score (single) imputed using the average distance control score from the last visit prior to starting non-randomized treatment for IXT.
- All other subjects, including treatment crossovers, will be analyzed as in the primary analysis.

Additional sensitivity analyses may be conducted to explore the effect of the methods for handling subjects with missing data and subjects who received non-randomized treatment for IXT before 12 months.

5.1.2 Secondary Distance Control Outcomes at 12 Months (On-Treatment)

Additional details of the secondary analyses in section 5.1.2.1 and 5.1.2.2 below will be part of a separate statistical analysis plan.

5.1.2.1 **No Spontaneous Tropia at 12 Months**

The proportion of subjects with no spontaneous tropia at 12 months will be compared between treatment groups using a two-sided Barnard's test with alpha of 0.05, with calculation of a two-sided 95% confidence interval on the difference in proportions.

No spontaneous tropia at the 12-month primary outcome exam means both of the following must have been true during the examination:

- Score of ≤2 (2 or better) on all three assessments of control at distance and at near
- No spontaneous tropia at any time during the exam at distance or near

An additional secondary analysis will assess this outcome according to whether these criteria were met at baseline, and according to subgroups based on severity of baseline distance control.

5.1.2.2 **Change in Distance Control at 12 Months**

Distance control will be reported as the distributions of baseline control, 12-month control, and change in control from baseline to 12 months, including % with ≥1 point change in control, ≥2 points change, etc.

The proportion of subjects with ≥1 point improvement in distance control between baseline and 12 months will be compared between treatment groups using a two-sided Barnard's test with alpha of 0.05, with calculation of a two-sided 95% confidence interval on the difference in proportions. The proportion of subjects with ≥2 points improvement in distance control between baseline and 12 months will be compared similarly.

5.2 Objective #2: Efficacy of Overminus After Treatment Discontinuation (18 Months)

The secondary objective is to assess the efficacy of overminus lenses after a period of weaning and discontinuation.

Treatment group comparisons of mean distance control, the proportion of subjects with no spontaneous tropia, and change in distance control from baseline (section 5.1) will be repeated using the 18-month (off-treatment) data.

These analyses will be performed on the full cohort which includes subjects who were and those who were not prescribed weaning of overminus between 12 to 15 months. In addition, these analyses will be repeated limiting to subjects who were prescribed weaning (i.e. prior to weaning being discontinued per Protocol Amendment II). If retention of an on-treatment effect is stronger in subjects who have full weaning vs. less than full weaning, the 18-month treatment effect could be diluted in the full cohort analysis vs. the limited cohort. The full cohort analysis will be considered the primary analysis for objective #2.

5.3 Additional Analyses

Each additional analysis in this *section* will be conducted for both the 12-month on-treatment and 18-month off-treatment time points. The details of the additional analyses will be part of a separate statistical analysis plan.

5.3.1 Additional Secondary Outcomes

Analysis of near control, angle magnitude, stereoacuity, and treatment compliance will be performed as described below.

5.3.1.1 **Deterioration**

At both the 12-month and 18-month time points, the cumulative proportion of subjects who meet either of the deterioration criteria (*section 3.7*) by the time point will be estimated for each treatment group using the proportional hazards model to enable adjustment for potential residual confounding. The adjusted cumulative probability estimate will then be compared between treatment groups using the Z-test. The cumulative proportion of patients who meet stereoacuity deterioration criteria by the time point and the cumulative proportion of patients who have constant exotropia by the time point will also be estimated and compared between treatment groups using similar methods. Analytic methods which account for possible informative censoring will be explored for handling subjects who start non-randomized treatment for IXT. Such methods will also be explored for the stereoacuity deterioration and motor deterioration outcomes.

5.3.1.2 **Near Control**

At both the 12-month and 18-month time points, near control will be evaluated similarly to the distance control primary analysis (*section 5.1.1*) and secondary analysis (*section 5.1.2*).

5.3.1.3 **Angle Magnitude**

At both the 12-month and 18-month time points, a two-sided comparison of magnitude of the deviation by Prism Alternate Cover Test (PACT) will be compared between treatment groups using an ANCOVA model, which adjusts for baseline PACT. The treatment group difference and a 95% confidence interval will be calculated. The analysis will be completed separately at distance and at near.

5.3.1.4 **Stereoacuity**

At both the 12-month and 18-month time points, a two-sided comparison of near stereoacuity by Preschool Randot Test will be compared between treatment groups using an ANCOVA model which adjusts for baseline stereoacuity. The treatment group difference and a 95% confidence interval will be calculated.

5.3.1.5 **Axial Length Measurement at 18 Months**

Mean 18-month axial length measurement will be compared between treatment groups using an ANOVA model. The treatment group difference and a 95% confidence interval will be calculated. Adjustment for baseline is not possible given that these measurements were added late in the study (with Protocol Amendment II), long after recruitment had ended.

5.3.1.6 **Additional Ocular Biometric Parameters at 18 Months**

Mean 18-months flat corneal radius, anterior chamber depth, and lens thickness will each be compared between treatment groups using an ANOVA model. The treatment group difference and a 95% confidence interval will be calculated. Adjustment for baseline is not possible given that these measurements were added late in the study (with Protocol Amendment II), long after recruitment had ended.

5.3.1.7 **Compliance with Spectacle Wear**

Compliance with spectacle wear will be assessed at the 6-month and 12-month outcome exam. Parents will give an estimate of the proportion of the time their children wore their spectacles. Proportion of time worn will be described as excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), or poor (≤ 25%). The distribution of compliance will be assessed for each treatment group at the outcome exam.

5.3.2 Exploratory Analyses

Exploratory analyses will be performed as specified below.

5.3.2.1 **Mean Distance Control in Baseline Subgroups**

The treatment group comparisons of 12-month and 18-month distance control will be assessed in subgroups based on baseline factors. The specific subgroups of interest include baseline distance control by severity, baseline age group (3 to <7 vs. 7 to <11), use of ADHD medications at any time between baseline and the 12-month visit (yes/no), and refractive error level. In accordance with NIH guidelines, subgroup analyses of treatment efficacy according to sex, as well as race/ethnicity, will also be conducted.

These planned subgroup analyses will repeat the primary analysis, including the baseline factor and the baseline factor by treatment interaction. In general, statistical power will be low for detection of interactions unless the interaction is very large.

Subgroup analyses will be interpreted with caution, particularly if the corresponding overall analysis does not demonstrate a significant treatment group difference.

5.3.2.2 **Mean Distance Control at 18 Months According to Prescribed Weaning Status**
Of the 355 expected 18-month visits (as of 11/5/19), approximately 283 subjects (80%) will have completed a full 3-months of prescribed weaning before discontinuing overminus (or non-overminus); approximately 35 to 54 (20% to 25%) subjects will have completed partial weaning, and approximately 18 to 37 subjects (5% to 10%) are expected to have no weaning at all, The summary statistics for and distribution of 18-month distance control will be tabulated according to treatment group and full, partial, or no prescribed weaning.

5.3.2.3 **Patients with Baseline Control 3 to <5 Points**
Exploratory analyses will be conducted limited to the cohort of subjects with baseline distance control 3-<5 points, a subset with better likelihood of improving ≥2 points and whose *mean* distance control at baseline is indicative of spontaneous tropia. It is noted that the remaining subjects (i.e., those with mean distance control scores at baseline <3 points) could potentially have shown a spontaneous tropia on one or two tests and still have a mean score <3 points.

At both the 12-month and 18-month time points, the distance control primary analysis (*section 5.1.1*) and secondary analysis (*section 5.1.2*) will be repeated using this cohort.

5.4 Safety Analyses

5.4.1 Refractive Error at 12 and 18 Months
Mean 12-month spherical equivalent refractive error will be compared between treatment groups using an ANCOVA model which adjusts for baseline spherical equivalent refractive error. The treatment group difference and a 95% confidence interval will be calculated.

5.4.2 Development of Esodeviation
Development of any esodeviation will be tabulated by treatment group, indicating the magnitude of the esodeviation (by PACT) and whether it was a constant tropia, intermittent tropia, or a phoria.

5.4.3 Reduction of Distance Visual Acuity
Any cases of reduced visual acuity in best refractive correction (≥2 logMAR lines) in either eye will be tabulated by treatment group.

5.4.4 Adverse Symptoms/Impact on Quality of Life
The distribution of scores on each quality of life questionnaire item and each symptom survey item will be described for the enrollment exam and the 6-month, 12-month and 18-month outcome exams for each treatment group. The distribution of change in scores will also be described for each treatment group.

5.5 Protocol Adherence and Additional Tabulations
The following tabulations and analyses will be performed:

- A flow chart accounting for all subjects according to treatment group for all visits.

- Visit completion rates for each follow-up visit according to treatment group.
- Protocol deviations according to treatment group.
- Baseline demographic and clinical characteristics according to treatment group
- Number of and reasons for unscheduled visits and phone calls
- Number of and reasons for non-randomized treatment according to randomized treatment group

Statistical tests will be performed as appropriate.

5.6 Interim Analysis

This study will include a separate interim monitoring plan that may incorporate monitoring for futility and/or efficacy for the 12-month on-treatment outcome (objective #1). The details of the formal interim monitoring plan will be developed in conjunction with the DSMC and incorporated into the statistical analysis plan prior to any tabulation or analysis of primary or secondary outcome data.

5.7 Sample Size

Sample size has been calculated for both the primary12-month on-treatment objective and the secondary 18-month off-treatment objective.

5.7.1 Sample Size for Objective #1: Efficacy on Overminus Treatment

Sample size has been calculated for both primary and secondary outcomes for the determining the efficacy of overminus lenses after 12 months of treatment.

Primary Outcome – Comparison of Mean Distance Control at 12 months

Sample size calculations have incorporated data from the IXT3 pilot RCT comparing observation vs. overminus. In the pilot study, 8-week mean distance control was 2.0 points in the 27 children treated with overminus spectacles vs. 2.8 points in the 31 children who were observed without treatment (adjusted difference = -0.75 (-1.42 to -0.07) point; P = 0.01 for one-sided test). Standard deviation of 8-week distance control in IXT3 was 1.5 points (95% CI = 1.2 to 1.8 points) and the correlation between baseline and 8-week distance control was 0.25 (95% CI = -0.02 to 0.47).

Reducing this -0.75 point 8-week on-treatment effect in the IXT3 pilot study to -0.65 points (to account for potential regression to the mean in the treatment effect observed in the pilot study) is thought to be a reasonable estimate of the 12-month on-treatment effect of overminus, given that many clinicians suspect the on-treatment effect to be reasonably constant over time. Assuming a conservative standard deviation of 1.8 points and using a 2-sided t-test with alpha = 0.05 and 90% power, a sample size of 326 subjects (163 per treatment group) is needed to detect a mean difference in distance control scores (overminus – non-overminus), at 12 months, if the magnitude of true mean difference is -0.65 points or larger (Table 3). An adjustment of the sample size by a factor of (1-Pearson's r^2) to account for the variance reduction expected from including baseline distance control scores in the ANCOVA analysis was considered but ultimately rejected given that the correlation between baseline and 12-month distance control might be expected to be less than the 0.25 correlation observed between baseline and the much-shorter 8-week outcomes in the IXT3 pilot study (also, it reduces sample size by fewer than 20 patients overall). Accounting for up to 10% loss to follow-up over 12 months, the sample size *for this objective* would be **364 subjects overall (182 per group)**

Table 3: Total Sample Size for Difference in Mean Distance Control Score at 12-Months

Standard Deviation of Outcome Distance Control (points)	Treatment Effect for 12-Month On-Treatment Outcome Distance Control (Overminus – Observation) (points)											
	-0.40	**-0.45**	**-0.50**	**-0.55**	**-0.60**	**-0.65**	**-0.70**	**-0.75**	**-0.80**	**-0.90**	**-1.0**	**-1.25**
1.2	382	302	246	204	172	146	126	110	98	78	64	42
1.3	466	354	288	238	200	172	148	130	114	90	74	48
1.4	518	410	332	276	232	198	172	150	132	104	86	56
1.6	676	534	434	358	302	258	222	194	172	136	110	72
1.8	854	676	548	454	382	326	280	246	216	172	140	90
1.9	952	752	610	504	424	362	312	272	240	190	154	100
2.0	1054	834	676	558	470	400	346	302	266	210	172	110

Cells indicate N for the overall study (both treatment groups combined), using a 2-sided test and alpha = 0.05.

Secondary Outcome – No Spontaneous Tropia at 12 Months

The proportion of subjects with a control score of 2 or better on all three 8-week distance control assessments in IXT3 was 67% in the overminus group vs. 42% in the observation group (difference = 25%; 95% CI = -2% to 49%); therefore, a conservative estimate of the true difference in the proportion of subjects with no spontaneous tropia might be 15%.

Accounting for up to 10% loss to follow-up over 12 months, the total sample size of 364 would provide 74% power to detect a difference if the true difference in the proportion of subjects with a control score of 2 or better on all three 8-week distance control between treatment groups was 15% or larger; the maximum width of the 95% confidence interval on an observed 15% difference in proportions between treatment group would be ±11%.

5.7.2 Sample Size for Objective #2: Efficacy of Overminus After Treatment Discontinuation

Primary Outcome – Comparison of Mean Distance Control at 18 Months

The IXT3 pilot study of overminus treatment did not have an off-treatment period on which to base estimates of the 18-month off-treatment effect. Because the 18-month off-treatment effect could potentially be smaller or larger than the 12-month on-treatment effect, using the same -0.65 point estimate (*section 5.6.1*) was felt reasonable.

Under the same assumptions for the 12-month outcome (assuming a conservative standard deviation of 1.8 points and using a 2-sided t-test with alpha = 0.05 and 90% power), a sample size of 326 subjects (163 per treatment group) is needed to detect a mean difference in 18-month distance control scores (overminus – non-overminus) if the magnitude of true mean difference is -0.65 points or larger**.**

Accounting for up to 10% loss to follow-up expected in the first 12 months of the study, and up to 5% additional loss to follow-up between 12 to 18 months, the total sample size is **384 subjects overall (192 per group).**

Secondary Outcome – No Spontaneous Tropia at 18 Months

Because the 18-month off-treatment effect could potentially be smaller or larger than the 12-month on-treatment effect (*section 5.6.1),* the same 15% difference in proportion of patients with no spontaneous tropia is assumed.

Accounting for up to 15% loss to follow-up over 18 months, the total sample size of 384 would provide 74% power to detect a difference if the true difference in the proportion of subjects with a control score of 2 or better on all three 8-week distance control between treatment groups was 15% or larger; the maximum width of the 95% confidence interval on an observed 15% difference in proportions between treatment group would be ±11%.

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