Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial

Protocol version 1.8

20 Aug 2020

ClinicalTrials.gov identifier: NCT02623426

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Phase 3 study

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Sponsor-investigator
Janet Holbrook, PhD, MPH
Director, MUST Coordinating Center
Professor of Epidemiology
Johns Hopkins Bloomberg School of Public Health
415 N. Washington Street, 2nd Floor
Baltimore, MD 21231

Medical Safety Officer
Akrit Sodhi, M.D., Ph.D.
Assistant Professor of Ophthalmology
Retina Division
Smith 4039
Wilmer Eye Institute
Johns Hopkins Medical Institutions
400 North Broadway Street
Baltimore, MD 21231

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Document revision history

22 Dec 2015

Title page

Added ClinicalTrials.gov Identifier: NCT02623426

Abstract

Corrected typographical error and divided last sentence into 2 to define the secondary outcomes.

1.4 Study centers and investigators

Clinic Director at University of Pennsylvania changed from John Kempen, MD, PhD to Nirali Bhatt, MD

1.8 Rationale for trial

Changed "uveitic macular edema persistent after intravitreal *triamcinolone* injection" to "uveitic macular edema persisting after an intravitreal *corticosteroid* injection"

2.2 Hypotheses

Changed "uveitic macular edema persistent after intravitreal *triamcinolone* injection" to "uveitic macular edema persisting after an intravitreal *corticosteroid* injection"

3.3 Trial schema

Added intravitreal methotrexate at week 4 (M02) as needed; previously additional injection only was permitted at week 8 (M03) as needed (per recommendation of DSMC)

3.6 Eligibility

Inclusion criterion #3 (eye level) was revised to allow macular edema persisting after intravitreal corticosteroid injection (which includes intravitreal dexamethasone) rather than limiting to macular edema persisting after intravitreal triamcinolone as follows: Macular edema (ME) defined as the presence of macular thickness greater than the normal range for the OCT machine being used, regardless of the presence of cysts, following an intravitreal corticosteroid injection (≥ 28 days following intravitreal triamcinolone injection and ≥ 90 days following intravitreal dexamethasone implant injection)

Inclusion criterion #6 (eye level): At request of DSMC, italicized text was added to clarify that eye being treated with combination therapy is equivalent to use of two IOP-lowering medications as follows: Baseline intraocular pressure > 5 mm Hg and ≤ 21 mm Hg (current use ≤2 intraocular pressure-lowering medications and/or prior glaucoma surgery are acceptable — *note that an eye being treated with a combination therapy like Combigan is counted as being*

treated with two IOP-lowering medications, which means, for example, that an eye treated with Combigan and a prostaglandin analogue is not eligible for the trial;

Exclusion criterion #9 (eye level): As recommended by the DSMC, changed "uncontrolled" to "severe" glaucoma as follows: History of severe glaucoma as defined by optic nerve damage (cup/disc ratio of ≥ 0.9 or any notching of optic nerve to the rim);

4.1.1 Schedule of assigned treatment and 4.1.2 Additional injections
For intravitreal methotrexate added that additional injections are permitted as needed at weeks 4 and 8; previously additional injection as needed at week 8 only

4.2.3 Intravitreal methotrexate injection preparation and administration

Removed information and reference describing the use of frozen methotrexate preparations as requested by CC's IRB as reference from 1988 is out of date.

4.2.4 Intravitreal ranibizumab formulation, storage, and administration

Added: Preparation of injection as requested by CC's IRB

- Using aseptic technique, remove contents from the vial using a 5 micron, 19 gauge filter needle attached to a 1-cc tuberculin syringe. Remove filter needle and replace with the provided 30 gauge ½ inch needle for injection.

5.1 Safety reporting of adverse events – General overview
This section was revised to reflect timeframe for DSMC Medical Safety Officer's review of SAE reports as agreed upon at 8 Dec 2015 DSMC meeting. Any SAE reports of a subject death will be sent to DSMC Medical Safety Officer within 24 hours of receipt at the CC. Non-death SAE reports will be sent to the DSMC Medical Safety Officer within 7 days of receipt at the CC. The DSMC Medical Safety Officer will review each report to determine what, if any, additional actions are needed, including whether the other DSMC members need to be informed of the event immediately as opposed to waiting for the next DSMC meeting or conference call.

7.2 IRB/Protection of human subjects

Data and safety monitoring

- Corrected description of new member from "statistician" to "experienced methodologist for ophthalmic studies"
- Clarified that DSMC will meet at least twice a year, one of these meetings being in person and one by conference call and that additional meetings may be arranged at the request of the DSMC Chair and/or the NEI Project Officer.
- Revised timeframe for and clarified that the DSMC Medical Safety Officer will review all SAE reports between meetings as detailed in section 5.1

Typographical errors corrected throughout document

28 Mar 2016, version 1.1

1.4 Investigators and study centers

- Changed Principle Investigators for Washington University and University of Southern California
- Deleted : Southeast Clinical Research Associates, Charlotte Eye Ear Nose &Throat Associates, Charlotte, NC
- Added:
  - Mid Atlantic Retina, Wills Eye Hospital, Philadelphia, PA
  - Mayo Clinic, Rochester, MN
  - University of Pittsburgh Medical Center Eye Center, Pittsburgh, PA

3.3 Trial schema

- Revised retreatment schedule to specify *required* time points for retreatment if retreatment criteria are met and added *permitted* time points for retreatment
- Added minimum time separation between treatments to retreatment criteria

3.6 Eligibility criteria

- Changed "History of infectious uveitis" from eye-level exclusion criterion to patient-level exclusion criterion
- Added eye level exclusion: Torn or ruptured posterior lens capsule

4. Study treatment: section reordered and details added for clarity

- 4.1 Overview section added
- Preparation and administration of study treatment moved to section 5
- 4.2 Treatment schedule by treatment arm
  - 4.2.1 Intravitreal dexamethasone
    - Clarified that retreatment is required at M04 if retreatment criteria met
    - Added retreatment permitted at later time points if retreatment criteria met
  - 4.2.2 Intravitreal methotrexate
    - Clarified that retreatment is required at M02 and M03 if retreatment criteria met; also at M04
    - Added retreatment permitted at later time points if retreatment criteria
  - 4.2.3 Intravitreal ranibizumab
    - Clarified that retreatment is required at M04 if retreatment criteria met
  - 4.2.4 Retreatment criteria
    - Added minimum time separation between study treatments

5. Study treatment preparation and administration

- Added 5.1 General Requirements to specify who is permitted to administer study treatment and the order of procedures for bilateral injection
- 5.2 added standard pre-injection procedures for all study treatments
- 5.4.2 added details for administration of intravitreal methotrexate
- 5.5.3 added details for administration of intravitreal ranibizumab
- 5.6 added standard post-injection procedures and monitoring for all study treatments

Additionally, typographical errors were corrected throughout document.

2 August 2016, version 1.2

Global changes

- Maximum number of IOP lowering agents for eligibility and retreatment increased from 2 to 3
- Correction of typographical errors and minor text changes for sake of brevity/clarification

3.3 Trial schema

- Retreatment IOP criterion modified by increasing the number of IOP-lowering meds permitted from ≤2 to ≤3 as in: *≤ 25 mm Hg with ≤ 3 IOP lowering agents permitted*
- Minimum time before retreatment: Added clarifications that while the minimum *target* time between injections is 12 weeks for dexamethasone and 4 weeks for methotrexate and ranibizumab, re-injection is permitted as early as 5 days before these targets, i.e., re-injection is permitted as early as 79 days since previous dexamethasone injection and 23 days since previous methotrexate or ranibizumab injection.

3.6 Eligibility

Inclusion criteria

- 2, 3, 5, &6 - changed "28 days" to "4 weeks" for style consistency
- 3- Changed time following intravitreal dexamethasone from ≥90 days to ≥12 weeks for consistency with exclusion criterion # 15
- 5 - Removed upper limit of best corrected visual acuity (BCVA) for eye-level eligibility; revised criterion is BCVA better than 5/200
- 6 - Increased the maximum number of IOP lowering medications permitted from 2 to 3 as follows: Baseline intraocular pressure > 5 mm Hg and ≤ 21 mm Hg (current use ≤3 intraocular pressure-lowering medications and/or prior glaucoma surgery are acceptable —; note that combination medications, e.g., Combigan count as two IOP-lowering medications);

Exclusion criteria

- 5 & 6 - changed "28 days" to "4 weeks" for style consistency
- 3 - Added new patient-level exclusion: History of serous retinopathy in either eye
- 5 - Clarification added as italicized for exclusion: oral prednisone dose ≤ 10 mg per day *at baseline* that has not been stable for at least 4 weeks *(Note: If patient is off of oral prednisone at baseline (P01 visit), dose stability requirement for past 4 weeks does not apply)*
- 15 & 16 Changed exclusion for anti-VEGF agent and intravitreal methotrexate from administered in *past 12 weeks* to administered in *past 4 weeks*

4.1 [Treatment] overview

- Pregnancy testing required for women of childbearing potential before additional intravitreal injections of methotrexate or ranibizumab

4.2.4 Retreatment criteria

- Minimum time between treatments: reduced by 5 days as follows
  - Intravitreal dexamethasone pellet: retreatment permitted as early as 79 days following last treatment; "minimum target" remains 12 weeks
  - Intravitreal methotrexate: retreatment permitted as early as 23 days; "minimum target" remains 4 weeks
  - Intravitreal ranibizumab: retreatment permitted as early as 23 days; "minimum

target" remains 4 weeks

5. 2 Standard pre-injection procedures for all study treatments

- Added general requirements
  - Treatment administrator and assistant wear masks during injection procedure
  - Everyone (including patient) is asked not to talk during procedure (to decrease risk of endophthalmitis)
- In last paragraph "Examples of approaches that may be used in study participants with prior adverse reactions associated with povidone-iodine" removed last sentence suggesting investigator discuss with Protocol Chair if circumstance such that alternative approaches presented for use of povidone-iodine are non-viable.

5.3 Administration of intravitreal dexamethasone pellet; inserted following into bulleted instructions

- Mark injection site ocular surface 3.5-4.0 mm posterior to limbus
- Added instruction to displace the conjunctiva with a cotton top applicator held in non-dominant hand prior to injection

5.4.2 Administration of intravitreal methotrexate

- Added clarification/specification that 19 gauge needle is a filter needle

6.0 Guidelines for use of difluprednate and nepafenac ophthalmic suspension

- Revised guideline for use in study eye at baseline, from "dose should not be changed" to "drug should be stopped".

10 May 2017, version 1.3

1.4 "Investigators and study centers" changed to "Resource and clinical centers"

- Replaced list of clinical centers and investigators with note that Clinical Centers and Clinic Directors are listed in the MERIT Manual of Procedures in keeping with the convention that clinical centers are not listed in the protocol for multicenter trials with more than 3 clinical centers.

1. 5 Support

- Added clarification as italicized: Genentech will provide Lucentis and support for distribution *for clinical centers located in the U.S. only.*

3.3 Trial schema

- Added study definition of ME improvement: 20% decrease in central subfield thickness of the macula or normalization of macular thickness even if there is <20% reduction
- Added footnote to emphasize that* IOP criteria for initial injection of study treatment in eligible eye(s) is ≤21 mm Hg with ≤3 IOP-lowering agents

3.6 Eligibility criteria

Exclusion criteria

- Patient level exclusion criterion #2 changed

  From

  2. History of scleritis or keratitis of any type in either eye

To

2. History of infectious scleritis of any type in either eye*. (Note: History of noninfectious scleritis that has been active in past 12 months is an eye-level exclusion –see #11 below.)*
3. History of keratitis (with the exception of keratitis due to dry eye)in either eye;

- Eye level exclusion criterion added
  13. History of active noninfectious scleritis in past 12 months *(Note*: *History of noninfectious scleritis is acceptable if the last episode of active scleritis resolved at least 12 months prior to enrollment);*

4.1. Treatment overview

- Revised text under 3rd bullet to emphasize the different pre-injection IOP criteria for initial treatment vs. retreatment
- Added last bullet: Treatment according to the best medical judgment of study ophthalmologist is permitted as deemed necessary. Repeat injections given before the protocol specified time points (section 4.2.) or other deviations from the treatment protocol should be reported expeditiously to CC on Unanticipated Event (UA) form

4.2. Study treatment schedule and re-treatment criteria and subsections

- Added note for all study treatments: *IOP requirements for the initial injection are the same as for eye eligibility for the trial. If study treatment is initiated on the same day as eligibility is confirmed and treatment assigned, no additional IOP measurements are needed. If circumstances require patient to return to clinic for injection at a later date, IOP must be checked and IOP-lowering agents evaluated prior to injection. If the eligibility requirements are not met, the injection should not be given. If the treating ophthalmologist elects to proceed with assigned treatment per best medical judgment, the deviation from the protocol must be reported to CC on an Unanticipated Event (UA) form; the UA form should be submitted as soon as possible.*
- General formatting of subsections modified and information repeated for completeness and clarification within section, e.g., in sections 4.2.2 (intravitreal methotrexate) and 4.2.3 (intravitreal ranibizumab) a bullet "For women of child-bearing potential, negative pregnancy test required before all injections" was added even though this information was already included in the overview section and elsewhere in protocol.

5.1.2 Pre-injection IOP requirements

Added distinction between IOP requirement before initial injection ≤21 mm Hg vs. before retreatment injections ≤25 mm Hg (Although IOP for study eligibility has always been ≤21 mm Hg Hg with 3 or fewer IOP-lowering agents, this revision of the protocol explicitly states that IOP criteria ≤21 mm Hg with 3 or fewer IOP-lowering agents need to be met before the initial study treatment (as in cases when the initial study treatment is not administered on the day of enrollment but on a later date.)

5.4 Intravitreal methotrexate preparation and administration

5.4.1 Preparation of [intravitreal methotrexate] injection by research pharmacy

- 2 - clarified Sterile Water for Injection is to be preservative free
- 3
  - Added more detail to instruction for clarity and note that pharmacist may place appropriate administration needle on the syringe instead of a syringe cap

- Added clarification regarding volume fill: Volume fill – syringe fill of 0.5 mL is guideline. If research pharmacy's existing label/practice is to fill syringe with alternative amount, e.g., 0.4 mL, this practice is acceptable as it will not affect the volume (0.1 mL) or dose injected.

- 4 – Changed parenthetical from (dose=2 mg) to (0.5 mL=2 mg)
- Changed "filtered needle" to "filter needle" throughout

5.4.2 Administration of intravitreal methotrexate

- Second bullet
  - Deleted first subpoint (Drawing 0.2 mL into syringe…)
  - Revised new first (previously second) subpoint for clarity
  - Next subpoint - changed 100 µL to 0.1 mL
  - Added needle specifications – 30 or 32 gauge ½ inch needle

5.5.3 Administration of intravitreal ranibizumab (Lucentis)

- Second bullet,
  - Second subpoint - Changed "filtered needle" to "filter needle"; revised to allow range of needle gauge (30 or32), specify length of needle (1/2 inch) and deleted sentence: A 32-gauge needle may be used in place of the 30-gauge needle, if preferred.
  - Third subpoint: following "plunger advanced to" 50 µL was deleted and parentheses around 0.05 mL removed

Global: minor edits in reference to changes above and formatting and spelling corrections

18 July 2017, version 1.4

Abstract

Added recurrent as italicized below

The Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial will compare the relative efficacy and safety of intravitreal methotrexate, ranibizumab, and dexamethasone implant for persistent or *recurren*t macular edema.

1.8 Rationale for trial

Added recurrent macular edema to rationale for trial as indicated in italics below

The goal of the MERIT Trial is to compare the relative effectiveness of a repeat corticosteroid injection for persistent or recurrent macular edema in eyes with controlled inflammation (the current standard approach), versus each of the alternative non-corticosteroid modalities (intravitreal ranibizumab or intravitreal methotrexate) for the treatment of uveitic macular edema that is persistent or recurrs after an intravitreal corticosteroid injection.

2. 1 Objective

Added recurrent as italicized below

The MERIT Trial was designed to find out which intravitreal therapy offers the best balance of effectiveness and tolerability in treating persistent or recurrent uveitic macular edema in eyes with controlled uveitis, specifically by comparing the relative efficacy and safety of intravitreal ranibizumab (Lucentis®) and intravitreal methotrexate to intravitreal dexamethasone implant (Ozurdex®) for the treatment of persistent or recurrent uveitic macular edema.

2.2 Hypotheses

Added recurring as italicized below

(1) Intravitreal injections of methotrexate will have greater efficacy than intravitreal injections of the dexamethasone pellet as a treatment for uveitic macular edema persisting *or recurring* after treatment with an intravitreal corticosteroid injection.

(2) Intravitreal injections of ranibizumab will have greater efficacy than intravitreal injections of the dexamethasone pellet as a treatment for uveitic macular edema persisting *or recurring* after treatment with an intravitreal corticosteroid injection.

3.3 Trial schema

Revised retreatment criteria

From

Eye does not meet ME improvement definition (20% decrease in central subfield thickness of the macula or normalization of macular thickness even if there is <20% reduction) OR ME worsens at the specified time point OR eye has achieved normal central subfield thickness but with cystoid spaces in the 1 mm central subfield

To

Central subfield thickness greater than 1.1X upper limit of normal (330 μm for Zeiss and Topcon SD OCT and 352 μm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield

3.6 Eligibility criteria : modified inclusion criterion (eye-level) #3 replacing “an” with “most recent” as follows:

(3) Macular edema (ME) defined as the presence of macular thickness greater than the normal range for the OCT machine being used (see cut points below), regardless of the presence of cysts, following ~~*an*~~ *most recent* intravitreal corticosteroid injection (≥ 4 weeks following intravitreal triamcinolone injection or ≥ 12 weeks following intravitreal dexamethasone implant injection);

4.2.4 Retreatment criteria

Revised retreatment criteria

From

Macular edema status is one of the following

- ME does not meet the improvement definition (a 20% decrease in central subfield thickness of the macula or normalization of macular thickness even if there is <20% reduction)
- ME worsens at the specified time point
- Eye has achieved normal central subfield thickness but with cystoid spaces in the 1 mm central subfield

To

Macular edema warrants retreatment if **one or both** of the following criteria are present:

- Central subfield thickness greater than 1.1X upper limit of normal (330 μm for Zeiss and Topcon SD OCT and 352 μm for Heidelberg OCT)
- Cystoid spaces within 1 mm central subfield

7.1 Possible side effects and complications of dexamethasone

Added: Patients with diabetes could experience a transient elevation in blood glucose

10. Added section: Efficacy monitoring and stopping guidelines

11.2 IRB/Protection of human subjects – Data and safety monitoring
- Arrangement and wording in 3rd paragraph revised for readiblity
- Information on interim effectiveness analysis added to 3rd paragraph

Global edits
- Typographical errors corrected throughout
- Added "or recurrent"; "/recurrent" as applicable throughout

23 January 2018 and 16 February 2018*, version 1.5

**JHSPH IRB reviewed 23 Jan version and requested 2 small changes to MTX prep (deletion of "filter" needle which had been inadvertently included and of requirement for IVA seal on syringe) which were made and revision date changed to 16 Feb 2018.*

Title page

Dr. Holbrook's title and address were updated

3.3 Trial schema

Retreatment at M04 if retreatment criteria met changed from required to permitted at M04 for all treatment arms

3.6 Eligibility criteria

The numbering of the inclusion criteria, which had started with 6 instead of with 1, was corrected

4.2 Study treatment schedule and retreatment criteria

4.2.1 Added new subsection: Table of study treatment schedule by treatment assigned and study visit

4.2.2 Intravitreal dexamethasone pellet, 0.7 mg (Ozurdex)
4.2.3 Intravitreal methotrexate, 400 µg in 0.1 mL
4.2.4 Intravitreal ranibizumab (Lucentis), 0.5 mg in 0.05 mL

- These subsections were renumbered to accommodate addition of section 4.2.1 and reorganized to list treatment requirements/options by study visit, i.e., M01, M02, M03, and M04/subsequent visits, to improve clarity
- The treatment schedule for the M04 study visit was changed from *required* if retreatment criteria met to *permitted* if retreatment criteria met and the following clarification added:

  If there has been evidence of a treatment benefit but a participant meets retreatment criteria at the M04 visit, the participant should be encouraged to continue the assigned treatment. However, the participant may be treated according to the best medical judgment of the study ophthalmologist at the M04 and subsequent visits.

5.2 Standard pre-injection procedures for all study treatments

The requirement for use of a sterile eyelid speculum was changed to: Retract the eyelids and lashes away from the injection site and needle for the duration of the procedure (use of an eyelid speculum is optional)

5.3 Administration of intravitreal dexamethasone pellet (Ozurdex)
5.4.2 Administration of intravitreal methotrexate
5.5.3 Administration of intravitreal ranibizumab (Lucentis)

Under the first bullet in each of these sections, the italicized text was added: use…of a sterile eyelid speculum or equivalent*, i.e., retraction of the eyelids and lashes from the injection site*

5.4.1 Preparation of injection by pharmacy

Replaced compounding instructions based on University of Illinois/Chicago, Eye Infirmary Pharmacy, March 18, 2008 with compounding instructions based on Bascom Palmer Eye Institute Department of Pharmacy Extemporaneous Compounding Record for Methotrexate 400 mcg/0.1 mL Intravitreal Injection, 24 May 2016. The main differences are summarized in table below.

Summary of changes to MTX compounding instructions, MERIT protocol version 1.4 to 1.5		
	Protocol versions 1.4 and earlier (Reference: Eye Infirmary Pharmacy University of Illinois/Chicago, 2008)	Protocol version 1.5 (Reference: Bascom Palmer Eye Institute University of Miami, 2016)
0.22 micron filter	Required	Not required*
Diluent	Preservative-free sterile water for injection	Preservative-free sodium chloride 0.9% solution
Storage temperature	Not specified	2-8 ◦C
Beyond use date	8 hours	24 hours

*Based on USP 797, this is a low-risk compound; use of a 0.22 micron filter is not necessary to prepare a compound from 2 sterile solutions.

6. Guidelines for use of topical corticosteroids and NSAIDS

- Changed from "Guidelines for use of difluprednate and nepafenac ophthalmic suspension" to the more general "Guidelines for use of topical corticosteroids and NSAIDS"
- Old guidelines: Difluprednate (Durezol®) and nepafenac ophthalmic suspension (Nevanac®) should not be introduced as treatment during trial; If participant is using either drug in study eye(s) at baseline, it should be stopped at baseline.
- New guidelines for topical corticosteroids (new subsection 6.1)
  - In general should not be introduced during the trial
  - If used at baseline (M01), maintain current dose except as follows
    - Tapering and/or discontinuing for medical issues, e.g., elevated IOP or rapidly progressing cataract
    - Transient increase in dose to treat recurrence of anterior segment inflammation
- New guidelines for topical non-steroidal anti-inflammatory drugs

- In general should not be introduced during the trial
- If used at baseline (M01), maintain current dose except if tapering and/or discontinuation required for medical reason, e.g., corneal melting

Global edits

- Typographical and formatting errors were corrected.

16 March 2018, version 1.5

3.3 Trial schema

4.2 Study treatment schedule and re-treatmenet criteria

4.2.2 Intravitreal dexamethasone

Retreatment schedule for the dexamethasone arm revised as follows:

- Changed from *earliest retreatment permitted at 12 weeks (M04) if retreatment criteria met* to *retreatment required at 8 weeks (M03) if retreatment criteria met.*
- Minimum *target* for retreatment changed from 12 weeks to 8 weeks; *earliest permissible* retreatment changed from 79 to 51 days after previous treatment

11.2 IRB/Protection of human subjects

- Under Data and Safety Monitoring Committee removed the description of a voting member with expertise in medical ethics. The medical ethicist resigned from the committee in 2017 citing increase in institutional responsibilities.

Non-substantive changes

- Global replacement of "re-treatment" with "retreatment"
- Section 4.2 and subsections minimal and minor wording changes for consistency and clarity Corrections of typographical and formatting errors throughout

11 April 2019, version 1.6

Cover

Added Clinical Trials Registry – India

1.4 Resource centers

Added relocation information for Chairman's Offcie as of 1 Aug 2019

3.5 Secondary outcomes

Revised secondary outcomes to reflect the outcomes planned for inclusion in the manuscript reporting the primary results

- Added rate of IOP elevation of ≥24 mm Hg and ≥ 30 mm Hg; removed rate of IOP elevation of >21 mm Hg

- For resolution of macular edema, changed the criteria for normalization of macular thickness from "to within +2 standard deviations of the normative mean for the OCT machine used" to "<260 um on the standard scale"
- Removed the following outcomes and associated references
  - Inflammation graded using semi-quantititive scales
  - New onset posterior subcapsular (PSC) cataract or progression of pre-existing PSC (using the Age-Related Eye Disease Study [AREDS] scheme
  - Cost effectiveness
  - Visual function related quality of life

5.4.1 Preparation of [methotrexate] injection by pharmacy

Added italicized text: If an alternative preparation of methotrexate *(i.e., alternative compounding procedure, storage conditions or beyond use date)* is to be used, it must be reviewed by the MERIT Protocol Chairs *and/or Executive Committee* and approved by the clinic's governing IRB

5.5.1 Formulation of ranibizumab

Added a note that the volume fill for the ranibizumab vials donated by Genentech for U.S. clinical centers was changed from 0.3 mL to 0.23 mL beginning with the drug distributed in August 2018 but the vial size (0.3 mL) did not change.

10. Efficacy monitoring and stopping guidelines

The time point for the single pre-planned interim efficacy was changed from once 50% to 40% of participants have completed the 12-week visit (the primary outcome time-point). The type I error thresholds were adjusted accordingly to 0.00016 (from 0.00082) at the interim analysis and 0.02484 (from0.02418) at the final analysis, maintaining a global 0.025 error rate over the course of the trial based upon O'brien-Fleming boundaries.

11.1 Recruitment and informed consent procedures

Revised description of clinical centers from "the majority of which are in the US and 3 are international (Melbourne, Australia; London, England, UK; Montreal, Canada)" to "located in the United States, United Kingdom, Australia, Canada, and India".

16 December 2019, version 1.7

5.5 Intravitreal ranibizumab (Lucentis(formaulaiton, storage, and administration

Added that ranibizumab 0.5 mg dose prefilled syringe may be used; previously the protocol referred to only ranibizumab vials because the ranibizumab donated by Genentech for U.S. clinical centers was in vials.

8.4.7 **Product complaints**

Added new section addressing reporting requirement for any product complaints for study treatments.

20 August 2020, version 1.8

3.6 Eligibilty criteria, *patient-level inclusion criteria*

Deleted criterion numbered 4: Baseline fluorescein angiogram that, as assessed by the study ophthalmologist, is gradable for degree of leakage in the central subfield

3.8 Data collection table

Deleted the following:

- Fundus reflex images (for phakic eyes) at M01 and M07
- Fluorescein angiogram at M01

Abstract

Macular edema (ME) is the most common structural complication and cause of visual impairment and legal blindness in uveitis patients. Traditional approaches to the treatment of uveitic ME have included the use of regional corticosteroid therapy, delivered periocularly, including posterior sub-Tenon's and orbital floor injections, or via the intravitreal route. While corticosteroid injections may reduce ME and improve vision, the effect is often variable with a limited duration. Persistent or recurrent macular edema is a common occurrence and often requires repeated intravitreal injections of corticosteroids, which expose eyes to a significant risk of increased intraocular pressure ocular and cataract development. The often refractory nature of uveitic ME and its impact on visual function underscores the need to identify effective alternative medical therapeutic options. Recent pilot studies have shown intravitreal methotrexate (MTX) and intravitreal ranibizumab (Lucentis®, Genentech Inc., San Francisco, CA) to be promising treatments for uveitic ME, and intravitreal dexamethasone implant (Ozurdex®, Allergan, Irvine, CA) has recently been approved for uveitic ME in patients with non-infectious uveitis. In addition to being effective, intravitreal MTX and ranibizumab potentially may have less ocular side effects than corticosteroids, particularly less IOP elevation. However, the relative efficacy of these treatments is unknown. The Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial will compare the relative efficacy and safety of intravitreal methotrexate, ranibizumab, and dexamethasone implant for persistent or recurrent macular edema. MERIT is a parallel design (1:1:1), randomized comparative effectiveness trial with an anniversary close-out at the 6-month clinic visit. The primary outcome is percent change in central subfield thickness from the baseline OCT measurement to the 12-week visit. Secondary outcomes are: improvement of macular edema based upon the MUST-accepted definition of ME improvement; resolution of macular edema based on the MUST-accepted definition of ME resolution (i.e., return to normative mean +/-2 standard deviations of the central subfield measurement); improvement in best corrected visual acuity; adverse events (i.e., cataract and IOP elevation); cost-effectiveness.

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1.1. Title

Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial

1.2. IND

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Sponsor-investigator
Janet T. Holbrook, PHD, MPH, Director Coordinating Center
Johns Hopkins University Bloomberg School of Public Health
Baltimore, MD

1.3. Financial sponsor

National Eye Institute U10EY024526

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Resource centers

Center	*Director*
Chairman's Office Icahn School of Medicine at Mount Sinai ,New York, NY* Johns Hopkins Bloomberg School of Public Health, Baltimore, MD† * Through 31 Jul 2019 † As of 1 Aug 2019	Douglas A. Jabs, MD, MBA
Coordinating Center Johns Hopkins Bloomberg School of Public Health, Baltimore, MD	Janet Holbrook, PhD, MPH
Reading Center University of Wisconsin at Madison, Madison, WI	Michael Altaweel, MD

Clinical Centers and Principal Investigators are included in the MERIT Manual of Procedures

1.5. Support

Genentech will provide Lucentis® (Ranibizumab 0.5 mg per 0.05 mL) for clinical centers in the U.S. only and support its distribution to those clinical centers.

1.6. Background and significance

The uveitides consist of over 30 diseases characterized by intraocular inflammation.[1] Each of these diseases has its own features, course, treatments, and prognosis. Traditionally these diseases have been grouped by the primary site of inflammation as: 1) anterior uveitis (cells in

the anterior chamber); 2) intermediate uveitis (cells in the vitreous); 3) posterior uveitis (chorioretinal inflammatory lesions); and 4) panuveitis (inflammation in the anterior chamber, vitreous and the choroid/retina). Visual loss typically occurs due to structural complications of the uveitis, such as macular edema, cataract, glaucomatous optic neuropathy, epiretinal membrane formation, retinal neovascularization, and choroidal neovascularization. The frequency of visual impairment (generally defined as worse than 20/40) and blindness (generally defined as 20/200 or worse[2]) vary depending on the class of the uveitis and the specific uveitic disease. Among patients with anterior uveitis 19% will have visual impairment in at least one eye, whereas among patients with panuveitis as many as 59% may have visual impairment in at least one eye.[5] Uveitis is the 5th or 6th leading cause of blindness in the United States[3, 4] and accounts for ~10% of all blindness in the United Kingdom (Lightman, S, personal communication). Because the uveitides affect all ages, including children, they have a much greater potential for causing years of potential vision lost than age-related diseases. Estimates suggest that the cost of managing uveitis is on par with that of managing diabetic macular edema.[6] As such, the uveitides and their management represent a substantial health problem.

Management of Uveitis

The initial treatment approach to a given non-infectious uveitis depends on the anatomic class: anterior uveitis is treated with topical corticosteroids; intermediate uveitis often is treated initially with regional corticosteroid injections; and posterior and panuveitides often are treated with systemic corticosteroids and depending on the specific disease immunosuppressive agents.[1, 7] Even when systemic agents are used, regional corticosteroid injections often are used as supplemental therapy for persistent or recurrent macular edema, after the evident inflammation is controlled. The fluocinolone acetonide implant (Retisert®, Bausch & Lomb, Tampa, FL) is an alternative to systemic therapy that is similar to systemic therapy in terms of visual acuity outcomes, controls the inflammation better than systemic therapy, but has higher rates of ocular corticosteroid side effects, such as cataract and ocular hypertension. The implant may have a particular role for patients poorly tolerant of systemic medications and those in whom systemic therapy does not adequately control the intraocular inflammation.[3] Appropriate management of uveitis and its complications improve outcomes. Several studies have shown that control of inflammation results in better visual outcomes[8-11] and that better control of structural complications, such as macular edema, is also associated with better visual outcomes.[12, 13] As such, the proper management of uveitis and its complications is critical to maintaining/improving visual acuity among patients with uveitis.

Macular edema is the most common structural complication of uveitis and the leading cause of visual loss in patients with uveitis.[5, 14, 15] In the MUST Trial, macular edema was present in approximately 40% of eyes with uveitis on enrollment with a similar frequency for patients with intermediate uveitis, posterior uveitis, and panuveitis.[16-18] A retrospective study from two uveitis referral centers in the Netherlands reported a similar proportion with uveitic macular edema (40%) and that macular edema accounted for 41% of visual impairment.[5] Although some patients with intermediate uveitis (~25%) do not develop structural complications and do not need treatment, the presence of macular edema is the most common indication for treatment among these patients.[19, 20] Among patients with intermediate uveitis (e.g. pars planitis), a stepped approach is used in which regional corticosteroid injections (either periocular or intravitreal) are the first approach typically chosen.[20, 21] Control of macular edema and preservation of visual acuity can be accomplished with regional corticosteroid injections only in 30 to 50% of patients who need treatment. For patients treated with systemic agents, including those with posterior uveitis and panuveitis, approximately 50% of eyes with uveitic macular edema will have incomplete resolution of the edema (i.e. have “persistent macular edema”) despite apparent control of inflammation (defined as no inflammatory cells present in the

anterior chamber or vitreous and control of the chorioretinal inflammatory lesions), and these patients will require supplemental therapy for the macular edema. Regional (periocular or intravitreal) corticosteroid injections typically are used as supplemental therapy in these cases.[14, 15, 22-25] The proper management of uveitic macular edema is critical for the preservation of good visual acuity in patients with uveitis.

Uveitic Macular Edema

The pathophysiology of macular edema associated with uveitis is thought to be a consequence of increased vascular permeability from mediators released by inflammatory cells resulting in damage to the function of the vascular endothelium, retina, and retinal pigment epithelial cells and the subsequent accumulation of fluid into the macula, characteristically distributed in the outer plexiform layer of the retina.[26] Exactly which mediators are critical in the pathogenesis of inflammatory macular edema is incompletely understood. Corticosteroids have been the first line of treatment for noninfectious uveitis in general and of inflammatory macular edema in particular. Corticosteroids inhibit the phospholipase A2 pathway, interfere with the release of inflammatory mediators, and decrease vascular endothelial growth factor (VEGF) secretion.[27, 28] Models of experimental autoimmune uveoretinitis in rats and studies in humans with uveitis and macular edema show an increased concentration of VEGF in the aqueous humor.[29-32] VEGF is suspected to play a role in the loss of vascular integrity in the eye and is known to be induced by inflammatory cytokines, such as interleukin (IL)-1 and IL-6, which have been found to be elevated intraocularly among patients with uveitis.[32, 33] Furthermore, aqueous VEGF concentrations are significantly higher in those patients with uveitic macular edema than those without uveitic macular edema.[30] The recent use of intravitreally administered nonsteroidal medications with anti-inflammatory activity for the treatment of inflammatory macular edema, such as methotrexate, and those which inhibit VEGF activity, such as ranibizumab, offers potentially effective alternative treatment approaches to macular edema in this population and might obviate the well-known ocular side effects of corticosteroid-based therapies.

Therapeutic options for uveitic macular edema

The management of uveitic macular edema initially is directed toward treatment of the underlying inflammation with appropriate medical therapy. Control of the inflammation often results in resolution of the macular edema. Regional corticosteroid injections control the intraocular inflammation, as well as treating the macular edema, which is why they are the initial therapy for 30-50% of patients with intermediate uveitis who need treatment. For posterior and panuveitis, initial therapy typically is oral corticosteroids with immunosuppression as indicated. Because smoking appears to increase the risk of macular edema among those with uveitis, smoking cessation typically is advocated.[26, 34, 35] For those patients with persistent or recurrent macular edema, despite control of the evident inflammation, supplemental proposed medical treatments include regional corticosteroid injections, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), oral acetazolamide[36, 37], intravenous infliximab infusions[38], subcutaneous interferon-α[39-41], and intravitreal injections of VEGF inhibitors, such as ranibizumab[42]. Intravitreal methotrexate (MTX), an antimetabolite with apparent efficacy when systemically administered,[8, 11] also has been used in pilot studies for refractory uveitis and persistent macular edema.[26, 43-46] Regional injections of corticosteroids are the most frequently used treatments specifically for uveitic macular edema. Corticosteroid injections reduce macular edema and improve vision, but the effect has a variable duration.[47, 48] Pars plana vitrectomy or vitrectomy in combination with intravitreal corticosteroids have been investigated as treatment options for inflammatory macular edema unresponsive to medical therapy; however, the impact of this intervention is not clear, and a systematic review concluded that the efficacy of this treatment remains unproven.[49, 50] The frequently persistent/recurrent nature of uveitic macular edema, its impact on visual function, and the plethora of potential treatments

with limited data supporting their use underscore the need to identify effective therapeutic options and have high quality evidence to support management choices.

Regional injections can be given periocularly or intravitreally. For periocular injections both triamcinolone acetonide and the "depo" preparation of methylprednisolone (Depo-Medrol®, Pharmacia and Upjohn Company, Division of Pfizer, New York, NY) have been used, and the injections may be given as a posterior, superior sub-Tenon's injection (PST) or as an orbital floor injection (also known as a retrobulbar injection).[24, 25, 51-63] With respect to periocular injections, available nonrandomized, but comparative, data suggest similar success rate with both approaches.[64-66] With respect to the choice of drug, triamcinolone acetonide is used more often, as it is better tolerated if there is inadvertent intraocular injection. For intravitreal injections, initial studies were performed with the Kenalog® (Bristol-Myers Squibb, Princeton, NJ) preparation of triamcinolone acetonide, but more recently a preservative-free preparation of triamcinolone has been developed for intraocular use (Triesence) and is US Food and Drug Administration (FDA) approved for this approach. The estimated pharmacologic effect of a regional corticosteroid injection of triamcinolone, whether given by the periocular or intravitreal route, is approximately 3 months, although the duration of benefit in some patients with uveitis may be longer. The dexamethasone intravitreal pellet appears to have a pharmacologic effect for 5 months and is US FDA approved for the treatment of uveitis. Although periocular and intravitreal injections of triamcinolone are commonly used for uveitic macular edema, there is regional and specialty (retina specialists vs. uveitis specialists) variation in their use without any comparative studies to guide the choice. Similarly, there have been no comparative studies of intravitreal triamcinolone to the intravitreal dexamethasone pellet.

Periocular corticosteroid injections: A retrospective study from the Johns Hopkins Medical Institution of 126 patients (156 eyes) with uveitic macular edema who received a single periocular injection of corticosteroid reported clinical resolution of macular edema in 53% and 57% of eyes at one month and three months after the injection, respectively.[67] Of the 83 eyes that had resolution of macular edema at one month, 40% had recurrence of the macular edema at three months. Of the eyes with persistent macular edema at one month, 40 eyes were treated with additional periocular injections, with an additional ~60% of those eyes having a clinical response one month later, for an overall success rate of approximately 80%. Overall, a 3-line improvement in visual acuity was observed in 52% at one month and in 57% at three months. Side effects attributed to periocular corticosteroid injections included a rise in intraocular pressure (IOP) to >30 mm Hg in 19% (rate = 0.14/eye-year [EY]), newly diagnosed cataract in 10% (rate = 0.13/EY), and ptosis in 14% (rate = 0.09/EY). Another similarly-sized retrospective study (159 eyes) evaluating PST injections of triamcinolone for uveitic macular edema reported that a single injection posed a similarly low risk of IOP elevation and cataract progression over a mean follow-up period of 12 months; however these side effects increased with repeated injections.[68] As such, a single periocular injection of triamcinolone appears to be effective in ~50% of patients, and a second injection to have additional benefits. Nearly all the benefit was detected by one month after the injection with limited additional benefit over the ensuing two months. These data suggest that one month after a regional injection is a reasonable time frame for assessing the response to therapy.

Intravitreal corticosteroids: A retrospective case series from Moorfields Eye Hospital in London of 54 patients (65 eyes) evaluated intravitreal triamcinolone in patients with uveitic macular edema.[55] Uveitic macular edema and visual acuity improved in 83% of eyes with a mean 12-letter gain (2.4 lines) in best corrected visual acuity after a mean follow-up of 8 months. The most important side effect was raised IOP; 43% of eyes experienced an IOP rise >10 mm Hg. Although not strictly comparable, these data suggest that intravitreal triamcinolone may be superior to periocular triamcinolone for the treatment of uveitic macular edema, but that the

frequency of elevated IOP may be greater. Similarly, a non-randomized, historically controlled study comparing the ocular side effects of periocular triamcinolone to intravitreal triamcinolone for macular edema from various causes demonstrated a significantly increased frequency of IOP> 30 mm Hg and the more frequent need for anti-glaucoma medication among the intravitreal-treated eyes.[69] Studies of intravitreal triamcinolone for persistent macular edema after systemic therapy controls the evident inflammation, including those from Moorfields Eye Hospital, suggest clinical resolution of the macular edema in 85% of eyes. Collectively, these data suggest that the intravitreal route may be more effective than the periocular route for the management of uveitic macular edema, but that the intravitreal route may be associated with a greater rate of ocular corticosteroid side effects.[26,55,62,63] The major limitation of intravitreal triamcinolone are its corticosteroid-related adverse ocular effects. The frequency of cataract development has been reported to range from 15-30% after a single injection[70-73] and increase with repeated injections.[74, 75] Corticosteroid-induced IOP elevations have been reported to occur in 25% to 45% of patients[55, 70-72, 76] are dose dependent[77, 78] and may be more frequent among children.[47] In most instances, elevated IOP is transient and may be controlled with anti-glaucoma medications.[58, 79] Although the long-term prognosis of uveitic macular edema treated with repetitive intravitreal triamcinolone is uncertain, a recent report demonstrated improved best corrected visual acuity with no evidence of tachyphylaxis to repeated intravitreal injections of triamcinolone and no evidence of increased rates of IOP elevation after the first injection. However, cataract progression requiring surgery was seen in all phakic patients by the fifth injection.[80]

In an effort to address the limited duration of action of intravitreal triamcinolone, sustained release implants have been developed and approved by the FDA, including the dexamethasone implant, Ozurdex. This implant is a copolymer containing dexamethasone, lactic acid and glycolic acid, which releases dexamethasone over a six month period as it degrades slowly into carbon dioxide and water. It is administered as an office based injection into the vitreous cavity.[81-87] The safety and efficacy of a single intravitreal injection of two dexamethasone pellet doses (0.7mg and 0.35mg) was reported from the HURON study, a 26-week, phase III, prospective, multicenter, masked, sham injection-controlled, randomized clinical trial among 229 patients with noninfectious intermediate or posterior uveitis.[88] Patients were randomized 1:1:1 to receive the higher-dose (0.7mg) pellet, the lower-dose (0.35mg) pellet, or a sham injection. The primary outcome was control of vitreous inflammation. Although both implant doses were shown to be effective in controlling vitreous inflammation and in improving visual acuity, the higher dose implant proved to have a longer duration of action without a significant increase in untoward ocular side effects and is the dose currently in clinical use. At 8 weeks after injections, 43% of treated eyes versus 7% in the sham group had at least a 15-letter improvement from baseline best corrected visual acuity, and the proportion of eyes achieving this level of improvement was 2- to 6-fold greater in the dexamethasone pellet groups as compared to the sham group at each visit throughout the study period. Evaluation of macular edema was performed with time-domain OCT, and there was a significant decrease in the mean macular thickness for both treatment groups (-99 μm for the higher-dose group and -91 μm for the lower-dose group) when compared to the sham-treated group -12 μm, $P<0.004$) at the eight-week visit. The proportion of eyes with improvement and/or resolution of the macular edema were not reported. The percentage of eyes with IOP ≥25 mm Hg peaked at 7.1% for the higher-dose implant group, 8.7% for the lower- dose implant group, and 4.2% for the sham-treated group. At 26 weeks, there was no statistically significant difference in the occurrence of cataract among groups (15% higher-dose, 12% lower-dose, and 7% sham-treated) with no patient requiring cataract surgery. However, patients with a history of an elevated IOP related to topical or regional injection corticosteroids were excluded from this study, so the comparative rate of IOP elevation vs. intravitreal triamcinolone is uncertain. Subsequent small, retrospective case series

also reported that the dexamethasone pellet was effective in treating noninfectious posterior uveitis with outcomes including decreased inflammatory activity, improved visual acuity, and an improvement in macular edema as evidenced by a reduction in mean central retinal thickness on optical coherence tomography (OCT). However, these studies suggest that the duration of effect may be shorter (3-4 months) in clinical practice than that reported in the HURON trial.[89-91] Although the side effect profile of the dexamethasone pellet appears to be superior to that of intravitreal triamcinolone, the study design of the HURON trial limits the ability to compare results.

Differing methodologies and different enrollment criteria substantially hamper comparing the data from these different studies. One of the most substantial differences is the methodology used to evaluate macular edema. Clinical estimates of macular edema improvement are heavily influenced by visual acuity improvement and may overestimate the resolution rate and the apparent efficacy of interventions on macular edema. Fluorescein angiography and OCT measure somewhat different aspects of macular edema, vascular leakage and retinal thickness, respectively. Although the two methods correlate, the correlation is moderate, as compensated leakage may not result in thickening, and thickening may occur without evident leakage.[4] Of the three methods (OCT, fluorescein angiography, clinical examination), clinical examination is least likely to detect macular edema.[4] Visual acuity loss correlates better with retinal thickness than with the two-dimensional area of leakage.[92] Even though vision is influenced by multiple factors, such as media opacity, change in macular thickness on OCT correlate with visual acuity improvement[93], suggesting that as a single measure of macular edema response for comparative studies, retinal thickness on OCT is a good one.

Taken together these data suggest that intravitreal triamcinolone may be a more effective initial treatment than periocular triamcinolone, as the intravitreal route may be superior for the delivery of corticosteroids. However, the side effects of intravitreal triamcinolone may be greater than those of periocular triamcinolone. Finally, the intravitreal dexamethasone pellet may have lower rates of side effects than those of intravitreal triamcinolone. However, the limited comparability of the different studies, the lack of comparative trials, and the widespread variation in use of these different agents all suggest that a clinical trial is needed to guide management. Furthermore, a relatively short-term trial with macular thickness on OCT as a comparative measure may be adequate to evaluate relative efficacy. Somewhat longer-term follow-up (e.g. 6 months) is needed to evaluate the duration of response and the need for additional injections. The MUST Research Group is conducting the PeriOcular and INTravitreal corticosteroids for uveitic macular edema (POINT) Trial which was designed to evaluate the comparative effectiveness of periocular triamcinolone injections, intravitreal triamcinolone injections, and intravitreal injections of the dexamethasone pellet for the initial regional treatment of uveitic macular edema. POINT is funded by the same grant and is the companion study for the MERIT Trial.

Management of Persistent Macular Edema

Despite appropriate management, up to 50% of eyes with macular edema will not fully resolve and will have persistent macular edema.[16] Although these eyes often are treated with additional regional corticosteroid injections, not all patients will improve, and alternative agents have been explored. In addition, the occurrence of substantial rises in IOP (e.g. to 35-40 mm Hg), while uncommon, and to a lesser extent the occurrence of cataract, has prompted the search for alternative, non-steroid regional treatments. Two agents that have been investigated have been intravitreal methotrexate injections and intravitreal anti-VEGF injections, such as ranibizumab.

Methotrexate

Methotrexate is an antimetabolite, administered weekly either orally or parenterally, used extensively in the treatment of rheumatoid arthritis and used for uveitis requiring

immunosuppression, particularly juvenile idiopathic arthritis-associated chronic anterior uveitis. Intravitreal methotrexate has been used successfully in the treatment of primary intraocular lymphoma without the occurrence of substantial adverse ocular effects.[94, 95] A dose of 400µg/0.1 mL is well tolerated by the retinal tissue and remains in a therapeutic concentration for 48-72 hours.[96] Several case series have suggested efficacy for intravitreal injections of methotrexate (400µg/0.1 mL) for the treatment of chronic intermediate uveitis and posterior uveitis and for inflammatory macular edema.[97-100] A six-month pilot study of patients with active intermediate, posterior, or panuveitis from Moorfields Eye Hospital examined the effect of a single intravitreal injection of methotrexate on visual acuity and macular edema.[98] Overall, 87% (13/15) of patients responded with significantly improved visual acuity, significantly reduced macular thickness on OCT, and significantly reduced ocular inflammatory scores. The onset of action appeared to be within one week of administration with a mean duration of effect of four months. Visual improvements were similar to those seen with previous injections of intravitreal triamcinolone. Patients who underwent a second injection had a similar response. No patients had an increase in IOP. The only evident treatment related side effect was corneal epitheliopathy in one patient, occurring two months following the initial injection. These data suggest that intravitreal methotrexate may be effective for the treatment of uveitis and of uveitic macular edema and that it may have lower rates of the ocular side effects of elevated IOP and cataract. However, the relative merits of this approach vs. repeat injections of intravitreal triamcinolone are unknown.

Ranibizumab

Ranibizumab is a recombinant, humanized monoclonal antibody antigen-binding fragment (Fab) to VEGF, that neutralizes VEGF, and currently approved by the FDA for the treatment of choroidal neovascularization in age-related macular degeneration (AMD), diabetic macular edema, and macular edema associated with retinal vein occlusions. Bevacizumab (Avastin®, Genentech, Inc., San Francisco, CA), an anti-VEGF monoclonal antibody and the parent molecule of the Fab fragment ranibizumab, was initially approved for the treatment of colorectal cancer, and is being used off-label for indications similar to those for ranibizumab. Studies leading to ranibizumab's approval for macular degeneration demonstrated a very low incidence of cataracts, elevated IOP and other adverse events, thus making it an attractive option with regard to safety.[101, 102] The two-year results of the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) supports the use of either drug as primary therapy for choroidal neovascularization associated with AMD, and also suggests that modification of monthly–dosing regimens may be feasible.[103, 104] One potential advantage of using ranibizumab instead of bevacizumab is that it has been shown to be 5- to 20-fold more potent than full-length bevacizumab in bioassays measuring inhibition of human VEGF-induced endothelial cell mitogenesis.[105] Clinically, in CATT, monthly injections of ranibizumab were the most effective in terms of proportion of eyes without fluid on OCT.

The safety and efficacy of ranibizumab for the treatment of patients with diabetic macular edema and macular edema due to retinal vein occlusion have been demonstrated in clinical trials which led to US FDA approval for these indications.[106, 107] Two multicenter randomized double-masked sham injection-controlled clinical trials in adult patients with diabetic macular edema showed a significant improvement in best corrected visual acuity at 24 months in the ranibizumab-treated group compared to the group receiving sham injections. Mean change in central foveal thickness also was significantly better in ranibizumab-treated patients, with a mean decrease of 255 µm in central foveal thickness at 24 months in the ranibizumab group, compared with a 130 µm decrease in the sham injection group ($P < 0.0001$). Less than 5% of patients experienced an ocular adverse event, such as endophthalmitis, retinal detachment or vitreous hemorrhage, by 24 months. Ranibizumab also is approved for the treatment of macular edema following branch retinal vein occlusion.[108, 109] A phase III multicenter, randomized,

double-masked, controlled study followed by a 6-month observation period showed a significant improvement in best corrected visual acuity (18.3 letters from baseline) compared with the sham injection group (7.3 letters, P < 0.0001). A significant improvement in central foveal thickness also occurred in the ranibizumab group (decrease of 345 μm at 6 months), compared with the sham injection group (158 μm decrease, P < 0.001). The safety profile of ranibizumab was consistent with prior phase III clinical trials of ranibizumab in neovascular age-related macular degeneration, with a very low rate of endophthalmitis, retinal tear/detachment and arterial thromboembolic events. A second phase III trial on vein occlusion enrolled patients with macular edema following central retinal vein occlusion and showed similar efficacy and safety as the trial evaluating branch retinal vein occlusion.[110, 111]

The use of intravitreal anti-VEGF drugs has been explored for the treatment of uveitic macular edema, but has yet to be studied systematically for this indication. There have been two prospective uncontrolled studies evaluating the effect of intravitreal ranibizumab injections on macular edema in patients with controlled uveitis who failed regional corticosteroid injections. The first, performed at the University of California, San Francisco,[42] was a prospective, uncontrolled case series, in which patients with inactive uveitis and persistent macular edema who had failed periocular corticosteroid treatment were given intravitreal ranibizumab injections (0.5 mg) monthly for 3 months, followed by re-injection as needed for the presence of macular edema. The primary outcome was the mean change best corrected visual acuity from baseline to three months, and the secondary outcome was the mean change in central retinal thickness on OCT. At three months, the mean increase in acuity was 13 letters (2.5 lines), and the mean decrease in central retinal thickness was 357 μm. Both best corrected visual acuity and central retinal thickness improved significantly between baseline and three months (P=0.03 for each). Although most patients required re-injection, the treatment success was maintained at 6 months. There were no significant ocular or systemic adverse effects. Hence, intravitreal ranibizumab led to an increase in visual acuity and improvement in uveitis-associated macular edema in patients refractory to or intolerant of standard, regional corticosteroid therapy.

The second prospective study, conducted at the Bascom Palmer Eye Institute, was a study of patients with controlled noninfectious uveitis and persistent macular edema that tested the effect of monthly ranibizumab (intravitreal injections, with repeated injections determined based on increase or persistence of retinal thickening or of cystoid spaces). Mean best corrected visual acuity improvement over 12 months was 12 letters on a logarithmic visual acuity chart (P=0.02 for comparison with baseline) and mean reduction in central retinal thickness was 45% (P=0.006 vs. baseline).[112] These data are highly suggestive that intravitreal ranibizumab injections will be useful for the treatment of uveitic macular edema, but there are caveats. The sample size for both studies was small, so the side effect profile has to be inferred from the use of ranibizumab for other forms of macular edema and for neovascular AMD. However, the data set for the relative safely of ranibizumab is substantial and the side effects consistent across diseases. The second is that ranibizumab does not treat the inflammation[113] and appears to be most useful for persistent macular edema in patients with controlled inflammation, which is the type of patients treated in the pilot studies. This role is consistent with ranibizumab's known effect on vascular permeability and apparent lack of effect on inflammatory pathways.

Bevacizumab has also been investigated as an off-label treatment for uveitic macular edema.[114-117] In two retrospective case series, one of which was conducted at the Massachusetts Eye Research and Surgery Institute, intravitreal injections of bevacizumab were associated with a short-term significant improvement in uveitic macular edema as measured by OCT.[115, 116] However, neither study found a statistically significant improvement in visual acuity, and the magnitude of the improvement in macular thickness appeared to be less than that reported in

the previously cited studies with ranibizumab. As these studies were not prospective and did not follow an identical protocol for all patients, it is difficult to directly compare outcomes.

In sum, these data suggest that persistent macular edema despite therapy for the inflammation remains a problem. The typical treatment of reinjection with a regional corticosteroid has some benefit, but that alternate treatments may prove to be better either in terms of efficacy or of the side effect profile. The absence of any comparative trials in this situation is problematic for developing evidence-based guidelines for the management of uveitic macular edema. A randomized clinical trial evaluating the comparative effectiveness of another corticosteroid injection with the alternate treatments of intravitreal methotrexate and of anti-VEGF agents is needed.

1.7. Preliminary studies

The MUST Research Group is a multicenter, clinical trials research group focused on trials on the management of uveitis and its structural complications. The original MUST Trial was a comparative effectiveness of the fluocinolone acetonide implant to the conventional approach of oral corticosteroids and immunosuppression as needed for non-infectious intermediate, posterior, and panuveitis. The 2-year results have been published[16], and a long-term follow-up study is ongoing. Results of the MUST Trial most directly relevant to this protocol are the estimates of macular edema in eyes with intermediate, posterior, or panuveitis (~ 40%) on presentation, fraction of patients with bilateral disease (~ 25%), and the persistence of macular edema among eyes with uveitic macular edema (~50% overall)[16, 18].

Also relevant are the MUST data on the comparability of clinical observation, fluorescein angiography, and OCT for identification of uveitic macular edema[17]. These data show that visual acuity is more closely related to retinal thickness among patients with uveitic macular edema[92], and indicate that OCT outcomes are appropriate measures for clinical trials of uveitic macular edema. Two levels of response are possible: 1) resolution, a return to normal, typically normal thickness; and 2) improvement, a clinically meaningful change that may or may not return to normal, but is indicative of a response to therapy. Because of the proliferation of OCT machines with slightly different normal ranges, change in retinal thickness is best expressed as a percent change so that it is machine independent. Percent change in retinal thickness is analogous to approach used for visual acuity, where changes in the visual angle are used as clinical trials outcomes. Change in best corrected visual acuity on a logarithmic acuity chart (e.g. ETDRS charts) typically is used, and a change of >5 letters is greater than measurement variability and changes of >10 letters and > 15 letters often are used as outcomes in trials.[118]

Although previous data suggested that the inter-measurement variability of OCT, regardless of machine, was <10%, and that a 20% change in macular thickness was highly reproducible,[119-124] prior to the MUST Trial it was unclear what level of clinical change in macular thickness was clinically meaningful.[93] In order to determine the optimal threshold for considering macular thickness improved (and thereby macular edema), data from the MUST Trial were analyzed to determine the threshold for a change in retinal thickness on OCT that best correlated with a change in best corrected visual acuity.[93] There was a strong association between a 20% reduction in retinal thickness and 5-letter, 10-letter, and 15-letter improvements in best corrected visual acuity (P<0.0001 for the 5-letter change); the agreement for a 20% reduction in thickness and a 5-letter improvement in visual acuity was 83% (95% CI 70-93%). The 20% change appeared optimal on receiver operator characteristic curve analyses. The sensitivity, specificity, positive predictive value, and negative predictive value of a 20% decrease in retinal thickness for a 5-letter improvement in visual acuity were 72%, 93%, 79%, and 90%, respectively. After adjusting for baseline acuity, the mean difference in the improvement in best

corrected visual acuity for eyes with a ≥ 20% decrease in retinal thickness vs. those with a <20% decrease was 10.4 letters (P<0.01). These data suggest that retinal thickness on OCT can be used as a clinically meaningful outcome in trials of treatments for uveitic macular edema. Furthermore, the percent change threshold allows future trials to use newer OCT machines once the normal range has been determined, as the outcome (percent change) is machine independent. These data are supportive of the rationale for the outcomes chosen for the POINT and MERIT trials.

Much of the preliminary data for the MERIT Trial (and for the companion trial POINT) have been generated by MUST Research Group investigators. The data on periocular triamcinolone injections for uveitic macular edema were generated by the Johns Hopkins clinical center.[67] Several studies evaluating intravitreal triamcinolone injections for the treatment of uveitic macular edema were performed at Moorfields Eye Hospital by the investigators at the MUST clinical center in London, UK.[55] Preliminary data on intravitreal methotrexate also were generated by the MUST investigators at the MUST center in London[98, 99] Two of the studies evaluating intravitreal ranibizumab injections for persistent macular edema have been performed at MUST clinical centers[42, 114] Collectively the MUST investigators are leaders in the field of uveitis and have provided much of the information used to design the MERIT and POINT clinical trials.

1.8. Rationale for trial

Although regional corticosteroid injections reduce macular edema and improve vision in many patients, the effect is variable, and up to 50% of eyes with uveitic macular edema have persistent edema, despite control of the inflammation.[16] Furthermore, the ocular side effects, of increased IOP and cataract formation, have been reported in a substantial proportion of patients treated with regional corticosteroid injections, and an increase in the risk of such side effects (e.g. cataract formation) may increase with multiple injections.[73, 78, 125] Hence there is a need for alternative agents with a different side effect profile (or lower rates of side effects). Ranibizumab is a recombinant, humanized monoclonal antibody that is FDA-approved for the treatment of choroidal neovascularization in AMD, diabetic macular edema, and macular edema after retinal vein occlusion.[101-105, 126] Phase III studies leading to ranibizumab's approval for AMD and post-marketing surveillance data demonstrate a low incidence of cataracts, and elevated IOP, suggesting favorable safety vis-à-vis corticosteroids. Pilot studies of ranibizumab for uveitic macular edema showed statistically and clinically significant improvements in both macular edema and best corrected visual acuity.[42] There is also evidence that intravitreal methotrexate, which also has a low rate of ocular complications, is a promising treatment for uveitic macular edema.[97-100] The goal of the MERIT Trial is to compare the relative effectiveness of a repeat corticosteroid injection for persistent or recurrent macular edema in eyes with controlled inflammation (the current standard approach), versus each of the alternative non-corticosteroid modalities (intravitreal ranibizumab or intravitreal methotrexate) for the treatment of uveitic macular edema that is persistent or recurrs after an intravitreal corticosteroid injection. Because many of these patients now are treated with the alternative corticosteroid (i.e. the dexamethasone pellet) rather than the reinjection of the same drug, the corticosteroid used for intravitreal injection in this study will be the dexamethasone pellet. The preliminary data suggest that alternative treatments (i.e., ranibizumab and methotrexate) may have greater efficacy in the situation. The MERIT Trial will be important in determining the role of these alternative non-corticosteroid intravitreal therapies in the treatment of uveitic macular edema persisting or recurring after successful control of the uveitis.

2. Objective and study hypothesis

2.1. Objective

The MERIT Trial was designed to find out which intravitreal therapy offers the best balance of effectiveness and tolerability in treating persistent or recurrent uveitic macular edema in eyes with controlled uveitis, specifically by comparing the relative efficacy and safety of intravitreal ranibizumab (Lucentis®) and intravitreal methotrexate to intravitreal dexamethasone implant (Ozurdex®) for the treatment of persistent /recurrent uveitic macular edema.

2.2. Hypotheses

(1) Intravitreal injections of methotrexate will have greater efficacy than intravitreal injections of the dexamethasone pellet as a treatment for uveitic macular edema persisting or recurring after treatment with an intravitreal corticosteroid injection.

(2) Intravitreal injections of ranibizumab will have greater efficacy than intravitreal injections of the dexamethasone pellet as a treatment for uveitic macular edema persisting or recurring after treatment with an intravitreal corticosteroid injection.

3. Design

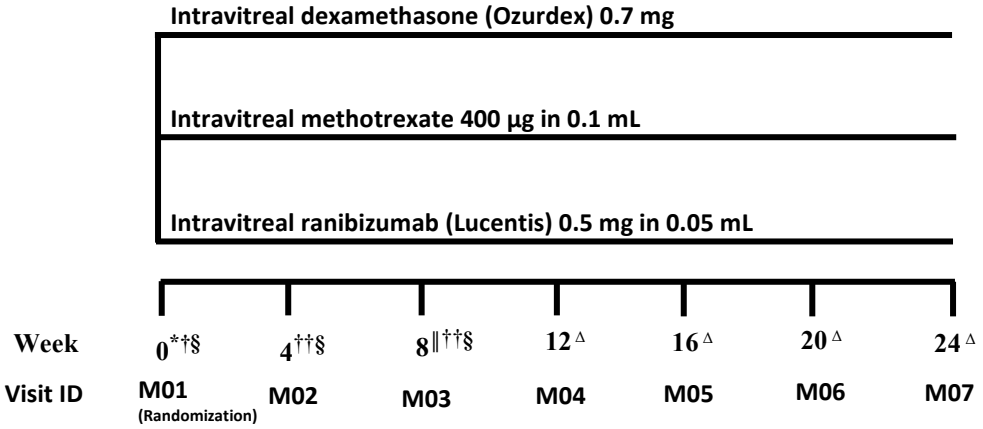
3.1. Type of study

- Randomized, three-arm, parallel design, randomized comparative effectiveness trial
- Randomization stratified by presence or absence of concomitant systemic corticosteroid and/or immunosuppressive therapy for any indication
- Unit of randomization is patient, not eye; if both eyes meet eligibility criteria, both receive same treatment
- Allocation ratio (1:1:1)
- Multicenter
- Fixed sample size, 240 (80 per treatment group)
- Anniversary close-out at the 6-month clinic visit
- Reading center graders and visual acuity examiners will be masked to treatment
- Treating physicians and patients will be unmasked (the intravitreal therapies are different in appearance and have potentially different injection schedules)

3.2. Treatment arms

- Ozurdex (0.7 mg dexamethasone pellet) delivered via intravitreal injection
- Methotrexate 400 µg in 0.1 mL via intravitreal injection
- Ranibizumab (Lucentis) 0.5 mg in 0.05 mL via intravitreal injection

3.3. Trial schema



Intravitreal dexamethasone arm

* Eligible eye(s) treated M01[+]

‖ Retreatment required at M03 if retreatment criteria met

Δ Retreatment permitted at M04 or later if retreatment criteria met

Intravitreal methotrexate arm

† Eligible eye(s) treated M01[+]

†† Retreatment required at M02, M03 if retreatment criteria met

Δ Retreatment permitted at M04 and later if retreatment criteria met

Intravitreal ranibizumab arm

§ Eligible eye(s) treated at M01[+], M02 and M03

Δ Retreatment permitted at M04 and later if retreatment criteria met

Retreatment criteria

1) Central subfield thickness greater than 1.1X upper limit of normal (330 µm for Zeiss and Topcon SD OCT and 352 µm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield.
2) IOP of <25 mm Hg (treatment with ≤3 IOP-lowering agents permitted)

[+] IOP critteria for initial injection of study treatment in eligible eye(s) is ≤21 mm Hg with ≤3 IOP-lowering agents

Minimum time between injections

- Intravitreal dexamethasone: minimum *target* 8 weeks after last injection but re-injection *permitted* as early as 51 days after last injection;
- Intravitreal methotrexate: minimum *target* 4 weeks after last injection but re-injection *permitted* as early as 23 days after last injection
- Intravitreal ranibizumab: minimum *target* 4 weeks after last injection but re-injection *permitted* as early as 23 days after last injection

3.4. Primary outcome

The primary outcome is the percent change in central subfield thickness from the baseline OCT measurement at the 12-week visit. The assessment of OCT outcomes will be performed by masked readers. The 12-week visit was chosen as the time to assess the primary outcome because the ranibizumab treatment arm specifies injections at baseline (i.e., post-randomization), 4 weeks and 8 weeks in all participants, and because the peak benefit for the dexamethasone pellet appears to be at the 8 to 12 weeks.

3.5. Secondary outcomes

- Rates of IOP elevation of ≥24 mm Hg, ≥30 mm Hg, and ≥ 10 mm Hg from baseline during the 24 weeks of follow-up
- Percent change in macular thickness as measured by OCT over the 24 weeks of follow-up
- Proportion of eyes with macular edema events over the 24 weeks of follow-up
  - ≥20% reduction in macular thickness (or normalization of macular thickness even if there is <20% reduction)
  - ”Resolution”, defined as normalization of the macular thickness, i.e., <260 um on the standard scale Worsening defined as a 20% increase in macular thickness from the lowest value after an injection
  - “Recurrence” defined as >20% increase in the central subfield measurement on OCT to an abnormal value in an eye that previously had resolution of ME
- Mean change in BCVA over the 24 weeks of follow-up.
  Best-corrected visual acuity score will be measured at every study visit under standardized lighting conditions by certified study examiners masked to study treatment using logarithmic (ETDRS) visual acuity charts, according to the method described by Ferris, et al.[127]
- Safety outcomes including elevated IOP (>30 mm Hg thresholds); vitreous hemorrhage; retinal tear/detachment; endophthalmitis; severe vision loss (≥15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) during the 24 weeks of follow-up.
  .

3.6. Eligibility criteria

Inclusion criteria:

Patient level inclusion criterion

1. 18 years of age or older;

Eye level inclusion criteria - at least one eye must meet all of the following conditions

2. Inactive or minimally active non-infectious anterior, intermediate, posterior or panuveitis, as defined by SUN[2] criteria as ≤ 0.5+ anterior chamber cells, ≤ 0.5+ vitreous haze grade and no active retinal/choroidal lesions for a minimum of 4 weeks;

3. Macular edema (ME) defined as the presence of macular thickness greater than the normal range for the OCT machine being used (see cut points below), regardless of the presence of cysts, following most recent intravitreal corticosteroid injection (≥ 4 weeks following intravitreal triamcinolone injection or ≥ 12 weeks following intravitreal dexamethasone implant injection);

   Greater than 300 µm for Zeiss Cirrus
   Greater than 320 µm for Heidelberg Spectralis
   Greater than 300 µm for Topcon 3DOCT

4. Best corrected visual acuity (BCVA) 5/200 or better;

5. Baseline intraocular pressure > 5 mm Hg and ≤ 21 mm Hg (current use of ≤3 intraocular pressure-lowering medications and/or prior glaucoma surgery are acceptable *(Note: combination medications, e.g., Combigan, are counted as two IOP-lowering medications);*

6. Media clarity and pupillary dilation sufficient to allow OCT testing and assessment of the fundus.

Exclusion criteria:

Patient level exclusion criteria

1. History of infectious uveitis in either eye;

2. History of infectious scleritis of any type in either eye *(Note: History of noninfectious scleritis that has been active in past 12 months is an eye-level exclusion –see #13 below)*;

3. History of keratitis (with the exception of keratitis due to dry eye) in either eye;

4. History of central serous retinopathy in either eye;

5. Active infectious conjunctivitis in either eye;

6. Oral prednisone dose > 10 mg per day (or of an alternative corticosteroid at a dose higher than that equipotent to prednisone 10 mg per day) OR oral prednisone dose ≤ 10 mg per day at baseline that has not been stable for at least 4 weeks *(note: if patient is*

off of oral prednisone at baseline (M01 study visit) dose stability requirement for past 4 weeks does not apply);

7. Systemic immunosuppressive drug therapy that has not been stable for at least 4 weeks *(note: use of systemic methotrexate is acceptable as long as regimen has been stable for at least 4 weeks)*;

8. Use of oral acetazolamide or other systemic carbonic anhydrase inhibitor at baseline;

9. Known allergy or hypersensitivity to any component of the study drugs;

10. For women of childbearing potential: pregnancy, breastfeeding, or a positive pregnancy test; unwilling to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for duration of trial;

Eye level exclusion criteria - at least one eye that meets all inclusion criteria cannot have any of the following conditions

11. History of infectious endophthalmitis;

12. History of severe glaucoma as defined by optic nerve damage (cup/disc ratio of ≥ 0.9 or any notching of optic nerve to the rim);

13. History of active noninfectious scleritis in past 12 months *(Note*: *History of noninfectious scleritis is acceptable if the last episode of active scleritis resolved at least 12 months prior to enrollment);*

14. Presence of an epiretinal membrane noted clinically or by OCT that per the judgment of study ophthalmologist may be significant enough to limit improvement of ME (i.e., causing substantial wrinkling of the retinal surface);

15. Torn or ruptured posterior lens capsule

16. Presence of silicone oil;

17. Ozurdex administered in past 12 weeks;

18. Anti-VEGF agent, intravitreal methotrexate, or intravitreal/periocular corticosteroid administered in past 4 weeks;

19. Fluocinolone acetonide implant (Retisert) placed in past 3 years.

3.7. Randomization

After the patient has given written informed consent, eligibility has been confirmed and baseline data have been keyed and passed an electronic eligibility review, the patient will be randomly assigned to one of the three treatment groups, via a web-based system, returning the treatment assignment result in real time. Beginning at this point, the patient's data will be included for primary analyses, regardless of subsequent actual treatment and/or extent of adherence to therapy. Randomization will be accomplished using an auditable, documented scheme

generating a reproducible order of assignment. Randomization schedules will be developed by the Coordinating Center (CC), using permuted blocks of varying lengths, designed to yield expected assignment ratio of 1:1:1. Randomization will be stratified by presence or absence of concomitant systemic corticosteroid and/or immunosuppressive therapy for any indication

3.8. Data collection schedule

Visit ID	**M01**	**M02**	**M03**	**M04**	**M05**	**M06**	**M07**
Time	**Baseline**	**4-wk**	**8-wk**	**12-wk**	**16-wk**	**20-wk**	**24-wk**
Medical/ophthalmic history	X	X	X	X	X	X	X
Treatment history	X	X	X	X	X	X	X
Best-corrected visual acuity	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X
Ophthalmic exam	X	X	X	X	X	X	X
Gonioscopy	X						
OCT	X	X	X	X	X	X	X
Health utility measures (EuroQOL, VFQ-25)	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X
Pregnancy testing	X†	X‡	X‡	X‡	X‡	X‡	X‡

† Required for all women of childbearing potential at M01

‡ Required for women of childbearing potential before any additional intravitreal injections of methotrexate or ranibizumab

4. Treatment schedule

4.1. Overview

- Study participants are randomized to receive one of three treatments in eye(s) meeting eye-level eligibility criteria at baseline (M01)

  Note: If only one eye is eligible at baseline then that eye will be the only study eye throughout the trial. If the second eye "meets eligibility criteria" later at a later time point, the second eye does not become a study eye. Rather the second eye is treated per best medical judgment of the study/ treating ophthalmologist.

- The timing of initial injections of assigned treatment, required 2nd and 3rd injections in ranibizumab group, and retreatment for all groups are specified in section 4.2 below

- All injections of study treatments must be administered per protocol instructions and follow relevant IOP pre-injection criteria
  - Initial injection of study treatment: IOP ≤ 21 mm Hg and ≤ 3 IOP-lowering agents
  - Retreatment: IOP <25 mm Hg and ≤ 3 IOP-lowering agents

- Pregnancy testing required for women of childbearing potential before additional intravitreal injections of methotrexate or ranibizumab

- Treatment according to the best medical judgment of study ophthalmologist is permitted as deemed necessary. Repeat injections given before the protocol specified time points (section 4.2.6) or other deviations from the treatment protocol should be reported expeditiously to CC on Unanticipated Event (UA) form.

4.2. Study treatment schedule and retreatment criteria

4.2.1. Table: Study treatment schedule by treatment assigned and study visit

Study treatment schedule by treatment assigned and study visit							
Treatment Assignment	**Study visits**						
	M01	**M02**	**M03**	**M04††**	**M05††**	**M06††**	**M07††**
	week 0	week 4	week 8	week 12	week 16	week 20	week 24
Ozurdex	Required	None	Required if criteria met*	Permitted if criteria met*†	Permitted if criteria met*†	Permitted if criteria met*†	Permitted if criteria met*†
Methotrexate	Required	Required if criteria met*	Required if criteria met*	Permitted if criteria met*	Permitted if criteria met*	Permitted if criteria met*	Permitted if criteria met*
Ranibizumab	Required	Required	Required	Permitted if criteria met*	Permitted if criteria met*	Permitted if criteria met*	Permitted if criteria met*

* ME retreatment criteria: Central subfield thickness greater than 1.1X upper limit of normal (330 um for Zeiss and Topcon SD OCT and 352 um for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield; IOP criteria <25 mm Hg (treatment with ≤3 IOP-lowering agents permitted)

† A minimum of 51 days is required between Ozurdex treatments so retreatment will be an option only if the last treatment was administered ≥51 days previously

†† Alternatively, participant may be treated according to the best medical judgment of the study ophthalmologist at the M04 and subsequent visits

4.2.2. Intravitreal dexamethasone pellet, 0.7 mg (Ozurdex)

- M01: Treatment required
  - Preferably administered on the day of randomization *but* may be administered up to 10 days after randomization
  - Pre-injection IOP requirements: ≤21 mm Hg and ≤3 IOP lowering agents*
- M02: No treatment
- M03: Retreatment required if criteria in section 4.2.5 are met
- M04 or a subsequent visit: Retreatment permitted if criteria in section 4.2.5 are met and if there has been at least 51 days since the last treatment.

  If there has been evidence of a treatment benefit but a participant meets retreatment criteria (see section 4.2.5) at the M04 visit, the participant should be encouraged to continue the assigned treatment. However, the participant may be treated according to the best medical judgment of the study ophthalmologist at the M04 and subsequent visits.

4.2.3. Intravitreal methotrexate, 400 µg in 0.1 mL

- M01: Treatment required
  - Preferably administered on the day of randomization but may be administered up to 10 days after randomization
  - Pre-injection IOP requirements: ≤21 mm Hg and ≤3 IOP lowering agents*

- M02: Retreatment required if criteria in section 4.2.5 are met

- M03: Retreatment required if criteria in section 4.2.5 are met

- M04 and subsequent visits: Retreatment permitted if the retreatment criteria in section 4.2.5 are met as discussed below and if there has been at least 23 days since the last treatment.

  If there has been evidence of a treatment benefit but a participant meets retreatment criteria at the M04 visit, the participant should be encouraged to continue the assigned treatment. However, the participant may be treated according to the best medical judgment of the study ophthalmologist at the M04 and subsequent visits.

- *For women of child-bearing potential, negative pregnancy test required before all injections*

4.2.4. Intravitreal ranibizumab (Lucentis), 0.5 mg in 0.05 mL

- M01: Treatment required
  - Preferably administered on the day of randomization but may be administered up to 10 days after randomization
  - Pre-injection IOP requirements: ≤21 mm Hg and ≤3 IOP lowering agents*

- M02: Treatment required
  - Pre-injection IOP requirement: <25 mm Hg and ≤3 IOP lowering agents

- M03: Treatment required
  - Pre-injection IOP requirement: <25 mm Hg and ≤3 IOP lowering agents

- M04 and subsequent visits: Retreatment permitted if criteria in section 4.2.5 and there has been at least 23 days since the last treatment. .

  If there has been evidence of a treatment benefit but a participant meets retreatment criteria at the M04 visit, the participant should be encouraged to continue the assigned treatment. However, the participant may be treated according to the best medical judgment of the study ophthalmologist at the M04 and subsequent visits.

- *For women of child-bearing potential, negative pregnancy test required before all injections*

** Note that the IOP requirements for the initial injection are the same as for eye eligibility for the trial. If study treatment is initiated on the same day as eligibility is confirmed and treatment assigned, no additional IOP measurements are needed.If*

circumstances require patient to return to clinic for injection at a later date, IOP must be checked and IOP-lowering agents evaluated prior to injection. If the eligibility requirements are not met, the injection should not be given. If the treating ophthalmologist elects to proceed with assigned treatment per best medical judgment, the deviation from the protocol must be reported to CC on an Unanticipated Event (UA) form; the UA form should be submitted as soon as possible.

4.2.5. Retreatment criteria and pre-injection IOP requirements

- Macular edema warrants retreatment if **one or both** of the following criteria are present:
  - Central subfield thickness greater than 1.1X upper limit of normal (330 µm for Zeiss and Topcon SD OCT and 352 µm for Heidelberg OCT)
  - Cystoid spaces within 1 mm central subfield

- IOP requirements pre-injection: <25 mm Hg and ≤ 3 IOP-lowering agents

- Negative pregnancy test required for women of childbearing potential before every injection of methotrexate or ranibizumab

4.2.6. Minimum time between treatments

- Intravitreal dexamethasone pellet
  - Minimum target for retreatment is 8 weeks
  - Retreatment is permitted as early as 51 days after last treatment

- Intravitreal methotrexate
  - Minimum target for retreatment is 4 weeks
  - Retreatment is permitted as early as 23 days after last treatment

- Intravitreal ranibizumab
  - Minimum target for retreatment is 4 weeks
  - Retreatment is permitted as early as 23 days after last treatment

4.3. Treatment failures

Eyes that demonstrate no improvement or worsening of ME as measured by the central subfield thickness on OCT at the 20-week visit (M06) are considered treatment failures and are to be treated according to best medical judgment of study/treating ophthalmologist.

5. Study treatment preparation and administration

5.1. General requirements

5.1.1. Study treatment administrator

Study treatments are to be administered by an ophthalmologist who is certified as either a MERIT study ophthalmologist or MERIT treatment administrator.

5.1.2. Pre-injection IOP requirements

- Pre-injection IOP
  - Before initial injection of study treatment in an eye: ≤21 mm Hg
  - Before retreatment injections: <25 mm Hg
- Use of 3 or fewer IOP-lowering agents *(note: a combination medication like Combigan is counted as two IOP-lowering medications)*

5.1.3. Bilateral study eye injections – order of procedures

If both eyes are study eyes and injections will be given in both eyes at the same visit

- All required injection procedures must be completed in the right eye prior to initiation of any pre-injection preparation of the left eye.
- The drug to be used in the left eye should not be present in the room prior to completion of all right eye injection procedures.

5.2. Standard pre-injection procedures for all study treatments

- General requirements
  - Treatment administrator and assistant wear masks during injection procedure
  - Everyone (including patient) is asked not to talk during procedure
- Treatment administrator and a second person confirm and mark study eye(s) to receive treatment
  - Confirm which is the study eye or eyes that is/are to receive the study treatment while directly viewing the Randomization (RZ) form that indicates the study eye or eyes
  - Mark that eye (or eyes) with a sticker or marking pen above the eye brow.
- Treatment administrator and a second person confirm that the drug obtained from the pharmacy matches the treatment assignment printout from the MERIT randomization system
- When the study participant is ready for the injection, apply at least one drop of topical anesthetic (solution or gel) to the eye
- Prepare eye for injection using the following sequence of steps:
  - Consider placing 2-3 drops of 5% povidone iodine in the lower fornix and/or using sterile cotton-tipped applicators soaked in 5% or 10% povidone iodine to swab the upper and lower eyelid margins and the upper and lower eyelashes (Optional)
  - Retract the eyelids and lashes away from the injection site and needle for the duration of the procedure (use of an eyelid speculum is optional)
  - Consider additional anesthesia with the application of one or two cotton-tipped applicators soaked in topical anesthetic over the intended injection site for at least 30 seconds. The use of lidocaine gel or other types of viscous anesthetic (e.g. TetraVisc™) is also permitted.

        - A subconjunctival anesthetic can be used in specific circumstances in which the study ophthalmologist believes that topical anesthetic is not sufficient to minimize discomfort
    - Encourage the study participant to look superonasally during the application of povidone iodine. Apply one of the following to the conjunctiva directly over and surrounding the intended injection site:
        - A cotton-tipped applicator soaked in 5% or 10% povidone iodine
        - A 10% povidone iodine Swabstick
        - At least 1-3 drops of 5% povidone iodine (at least enough to cover the intended injection site)
    - Allow 30-60 seconds for the povidone iodine to be in contact with the injection site before injection.
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.

NOTE: As indicated above, injection preparation must include the use of povidone-iodine either applied directly to the injection site using topical drops, a cotton-tipped applicator, or swabstick. If a study participant experiences an adverse reaction to povidone-iodine, other approaches to limit the exposure of povidone-iodine may be permitted. However, **a study participant may not receive an intravitreal injection without use of povidone-iodine directly to the injection site just prior to the injection.**

Examples of approaches that may be used in study participants with prior adverse reactions associated with povidone-iodine include using a limited amount of povidone-iodine by placing a swab directly on the injection site after the lid speculum has been placed or the eyelids and lashes have been retracted by other means, subsequently ensuring that nothing further touches that site before the injection. Alternatively, study ophthalmologist could consider using povidone-iodine and then gently irrigating the eye with sterile saline after the injection to try to rinse away any remaining povidone-iodine or gently applying a sterile cotton tipped applicator adjacent to the intended injection site to immediately absorb excess povidone-iodine that has been placed

5.3. Administration of intravitreal dexamethasone pellet (Ozurdex)

- Injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum or equivalent, i.e. retraction of the eyelids and lashes from the injection site and needle

After completing standard pre-injection procedures (section 5.2 above)

- Mark injection site ocular surface 3.5-4.0 mm posterior to the limbus
- Open the foil pouch over a sterile field and gently drop the applicator on a sterile tray
- Carefully remove the cap from the applicator.
- Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab.
- The long axis of the applicator should be held parallel to the limbus
- Displace the conjunctiva with a cotton tip applicator held in the non-dominant hand
- The sclera should be engaged at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path.
- The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of

the sclera is completed and the vitreous cavity is entered. The needle should not be advanced past the point where the sleeve touches the conjunctiva.

- Slowly depress the actuator button until an audible click is noted.
- Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface.
- Remove the needle in the same direction as used to enter the vitreous.
- *Follow standard post-injection procedures and monitoring (section 5.6 below)*

5.4. Intravitreal methotrexate injection preparation and administration

5.4.1. Preparation of injection by pharmacy

Methotrexate injections are to be prepared by a research/compounding pharmacy as detailed below.

Ingredients	Strength	Amount
Methotrexate preservative-free liquid vial	25 mg/mL	0.64 mL
Sodium chloride solution, preservative-free	0.9%	3.36 mL

Methotrexate is a cytotoxic agent. Use standard chemotherapy handling precautions in a biologic safety cabinet that provides a sterile environment when preparing this product.

Compounding procedure

1. From the methotrexate 1 g (25 mg/mL) liquid vial, withdraw 0.64 mL (16 mg) and transfer to a sterile empty vial. This is methotrexate vial B.
2. To methotrexate vial B, add 3.36 mL of Preservative-Free Sodium Chloride 0.9% solution and mix well.
3. From methotrexate vial B, withdraw 0.3 mL (0.1 mL desired dose plus 0.2 mL overfill)* of the solution into the syringe. Replace the needle with a syringe cap.
4. Label: Methotrexate 400 mcg/0.1 mL intravitreal injection (***Contains Overfill ***)
   * Volume fill – syringe fill of 0.3 mL is guideline. If research pharmacy's existing label/practice is to fill syringe with alternative amount, this is acceptable as it will not affect the volume (0.1 mL) or dose injected

Storage: Refrigerate (2-8°C);

Expiration: Beyond use date is 24 hours

Reference: Bascom Palmer Eye Institute Department of Pharmacy Extemporaneous Compounding Record for Methotrexate 400 mcg/0.1 mL Intravitreal Injection, 24 May 2016.

Additional information

- Prepared syringe is for single use (one eye only)
- Syringe with the excess methotrexate should be discarded in a biohazard container/chemotherapy bin per institutional guidelines
- If an alternative preparation of methotrexate is to be used (i.e., alternative compounding procedure, storage conditions or beyond use date), it must be reviewed by the MERIT Protocol Chairs and/or Executive Committee and approved by the clinic's governing IRB

5.4.2. Administration of intravitreal methotrexate

- Injection procedures should be carried out under controlled aseptic conditions which

include the use of sterile gloves and a sterile eyelid speculum or equivalent, i.e. retraction of the eyelids and lashes from the injection site

After completing the standard pre-injection procedures (section 5.2 above)

- The position of the injection site is 3.5mm-4.0mm posterior to the limbus; distance should be marked on ocular surface
- The study ophthalmologist/treatment administrator prepares the proper volume of drug to be injected as follows
  - Replace the sterile syringe cap with a sterile 30-gauge or 32-guage ½ inch needle
  - With the needle cap removed, expel fluid at an approximately 45-degree angle until the plunger is advanced to 0.1 mL
  - The syringe is now ready for injection
- Instruct participant to direct gaze away from syringe
- Inject the drug into the vitreous cavity pointing toward the optic nerve via the pars plana.
- Place a cotton swab on the site as the needle is injected to help prevent extrusion of medication
- *Follow standard post-injection procedures and monitoring (section 5.6 below)*

5.5. Intravitreal ranibizumab (Lucentis) formulation, storage, and administration

5.5.1. Formulation of ranibizumab

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile 0.3 mL stoppered glass vial or in a prefilled syringe. Each single-use vial or prefilled syringe is designed to deliver 0.05 mL of 10 mg/mL ranibizumab aqueous solution with 10 mM histidine HCl, 10%, a-trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. This results in the delivery of a 0.5 mg dose of ranibizumab. Each vial and prefilled syringe contains no preservative and is suitable for single use only. Either vials or prefilled syringes may be used.

Notes:

- *The volume fill for the ranibizumab vials donated by Genentech for U.S. clinical centers was changed from 0.3 mL to 0.23 mL beginning with the drug distributed in August 2018 but the vial size (0.3 mL) did not change]*
- *After Mar 2020, Genentech will provide ranibizumab for U.S. clinical centers as 0.5 mg dose prefilled syringes.*

5.5.2. Storage of ranibizumab

- Upon receipt, ranibizumab should be refrigerated at 2°C - 8°C (36°F - 46°F). DO NOT FREEZE
- Do not use beyond the expiration date
- Ranibizumab should remain refrigerated.
- Protect from direct light
- Store in original carton until time of use

Ranibizumab vials and prefilled syringes are for single use only. Vials or prefilled syringes used for one subject may not be used for any other individualt.

5.5.3. Administration of intravitreal ranibizumab (Lucentis)

- Injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum or equivalent , i.e. retraction of the eyelids and lashes from the injection site

After completing standard pre-injection procedures (section 5.2 above)

- The position of the injection site is 3.5mm-4.0mm posterior to the limbus; distance should be marked on ocular surface
- Preparation of proper volume of drug to be injected
  - If using ranibizumab vial, he study ophthalmologist/treatment administrator prepares the proper volume of drug to be injected by
    - Drawing 0.2mL into the syringe using a sterile 19-gauge filter needle.
    - The 19-gauge filter needle should then be removed and a sterile 30-gauge or 32-guage ½ inch needle should be placed onto the syringe.
    - With the needle cap removed, fluid is expelled at an approximately 45-degree angle until the plunger is advanced to 0.05 mL
    - The syringe is now ready for injection
  - If using ranibizumab prefilled syringe, the study ophthalmologist/treatment administrator prepares the proper volume of drug to be injected as follows
    - Remove syringe cap (snap off)
    - Attach a 30G x ½ inch needle and remove needle cap
    - Inspect for and dislodge any air bubbles by gently tapping on syringe
    - Expel air and adjust durg dose by pushinjg plunger until edge below rubber stopper is alrighed with the 0.05 mL dose mark
    - The syringe is now ready for injection

- Instruct participant to direct gaze away from syringe prior to intravitreal injection
- Inject the drug into the vitreous cavity pointing toward the optic nerve via the pars plana
- Place a cotton swab on the site as the needle is injected to help prevent extrusion of medication
- *Follow standard post-injection procedures and monitoring (section 5.6 below)*

5.6. Standard post-Injection procedures/monitoring for all study treatments

- Remove the lid speculum/unretract eyelid and lashes and avoid any excess pressure on the eye
- Post-injection topical povidone-iodine may be used over the injection site at the administrator's discretion
- Monitor for IOP elevation and assess for any other complications either via indirect ophthalmoscopy immediately after injection to confirm that the central retinal artery is perfused (even if it is pulsating) or a vision check to confirm that there is some perception of vision in the study eye (for example, able to count fingers or perceive hand motion or light perception) and/or tonometry within 15 minutes following injection.

6. Guidelines for use of topical corticosteroids and NSAIDs

Topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have potential treatment effects on macular edema. Use of these drugs in study eyes per the following guidelines is encouraged to minimize confounding.

6.1. Topical corticosteroids

- In general topical corticosteroids (e.g., difluprednate (Durezol®), prednisolone) should not be introduced during the trial
- Participants using a topical corticosteroid at baseline (M01) should be maintained at their current dose except as follows
  - Tapering and/or discontinuing is permitted for medical issues that may arise during the study, such as elevated IOP or rapidly progressive cataract
  - A transient increase in dose is permitted to treat a recurrence of anterior segment inflammation, with the goal of tapering down to the baseline dose

6.2. Topical non-steroidal anti-inflammatory drugs

- In general topical non-steroidal anti-inflammatory drugs (NSAIDs) should not be introduced during trial
- Participants using a topical NSAID at baseline (M01) should be maintained on their current dose except as follows
  - Tapering and/or discontinuing are permitted for a medical reason such as corneal melting

7. Possible side effects and complications of study treatments

7.1. Intravitreal dexamethasone

- Commonly reported events related to the drug
  - Elevated intraocular pressure (IOP) which may require medication to lower

- Less frequently reported events related to the drug
  - Short-term visual disturbances
  - Headache
  - Cataract development
  - Elevated intraocular pressure (IOP) which may require surgery to control
  - In eyes with non-intact posterior capsule, implant migration to anterior chamber
  - Patients with diabetes could experience a transient elevation in blood glucose

- Rare and serious events related to the drug
  - Perforation of the globe where there is thinning of the cornea or sclera

- *Possible side effects and complications related to intravitreal injections are listed in section 7.4*

7.2. Intravitreal methotrexate

- Commonly reported events related to the drug
  - Reversible corneal epitheliopathy

- Rare and serious events related to the drug
  - Sterile endophthalmitis

- *Possible side effects and complications related to intravitreal injections are listed in section 7.4*

7.3. Intravitreal ranibizumab

- Commonly reported events related to the drug
  - Mild visual disturbances
  - Transient IOP increase

- Rare and serious events related to the drug

  Potential risk of arterial thromboembolic events (ATEs. i.e., nonfatal stroke, nonfatal myocardial infarction, or vascular death). However, the rates in the Lucentis clinical trials were low. In two studies for treatment of macular edema following retinal vein occlusion, the ATE rate at 6 months was 0.8% for both the subjects treated with intravitreal ranibizumab (0.3 mg or 0.5 mg) and the control group. In studies for treatment of diabetic macular edema the ATE rates at 2 years were: 7.2% for subjects treated with 0.5 mg; 5.6% for 0.3 mg and 5.2 for control. Stroke rates were 3.2.%, 1.2% and 1.6%, respectively [128]. In a population based nested case-control

study intravitreal bevacizumab and ranibizumab were not associated with significant risk of ischemic stroke, acute myocardial infarction, congestive heart failure or venous thromboembolisms. [129]

- *Possible side effects and complications related to intravitreal injections are listed in section 7.4*

7.4. Intravitreal injection

Risks of an intravitreal injection stem from risks associated with the injection procedure itself. These risks apply to all injections of study treatment above.

- Commonly reported events related to injection procedure
  - Mild ocular discomfort or pain
  - Increased tearing
  - Subconjunctival hemorrhage
  - Conjunctival hyperemia
  - IOP elevation — typically transient not requiring therapy

- Less frequently reported events related to injection procedure
  - Mild short-term ocular discomfort
  - Vitreous detachment

- Rare and serious adverse reactions related to the injection procedure
  - Endophthalmitis
  - Retinal tear and/or rhegmatogenous retinal detachment
  - Eye inflammation
  - Vitreous hemorrhage
  - Vitreous detachment
  - Iatrogenic traumatic cataracts. [128, 130, 131]

8. Safety reporting of adverse and other events

8.1. General overview

Adverse events (AEs) will be recorded on study data forms and submitted to the CC. Serious adverse events (SAEs), which include death, all hospitalizations, life-threatening illness, overdose, or congenital abnormalities in the offspring of subjects, will be reported to the CC as SAE reports within 72 hours after clinical center personnel become aware of the event. An assessment will be made by the clinical investigator at the managing clinical center as to whether the event is related to treatment. Dr. Akrit Sodhi, the CC Safety Officer, and Dr. Alan Palestine, the DSMC Safety Officer, have been commissioned to review all adverse events and to make recommendations to the DSMC as to any actions that may be needed. All SAEs will be reported expeditiously regardless of the relationship of treatment. These reports will be sent to the CC Medical Safety Officer for immediate review and determination as to whether the event meets the criteria for a safety report. Any SAE reports of a subject death will be sent to DSMC Medical Safety Officer within 24 hours of receipt at the CC. Non-death SAE reports will be sent to the DSMC Medical Safety Officer within 7 days of receipt at the CC. The DSMC Medical Safety Officer will review each report to determine what, if any, additional actions are needed, including whether the other DSMC members need to be informed of the event immediately as opposed to waiting for the next DSMC meeting or conference call. All serious and unexpected events possibly related to study treatment will be reported as safety reports to the NEI project officer, the FDA, the pharmaceutical supplier (where appropriate), and all clinical centers in accordance with FDA regulations. The CC and clinical centers will submit all safety reports as expedited reports to their IRBs. Reports of AEs not deemed to be unexpected will be submitted to the CC IRB, to the IRB of the clinical center in which the event was reported, as well as to any other study center IRBs which require such reports.

Specific adverse event reporting requirements and instructions are detailed in the MERIT Manual of Procedures.

8.2. Assessment of Safety

8.2.1. Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to any of the study treatments (intravitreal dexamethasone pellet (Ozurdex); intravitreal methotrexate; intravitreal ranibizumab (Lucentis), all events of death, and any study specific issue of concern.

8.2.2. Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with uveitic macular edema that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions.

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

8.2.3. Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

8.3. Methods and timing for assessing and recording safety variables

The clinical center investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the Coordinating Center and their governing IRB. The Coordinating Center is responsible for reported events to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

8.3.1. Adverse Event Reporting Period

- The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment [or "initiation of any study procedures"] and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier.

- After this period, investigators should only report SAEs that are attributed to prior study treatment.

8.3.2. Assessment of Adverse Events

- All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately.

- Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study treatment (see following guidance), and actions taken.

- To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- Yes
  - There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies

  And/or
  - The AE follows a known pattern of response to the study treatment; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.
- No
  - Evidence exists that the AE has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication):

  And/or
  - The AE has no plausible temporal relationship to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study treatment).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

8.4. Procedures for eliciting, recording, and reporting adverse events

8.4.1. Overview

- Eliciting adverse events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

- Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

8.4.2. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.4.3. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

8.4.4. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

8.4.5. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

8.4.6. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 30 days after the last dose of a study treatment, a report should be completed and expeditiously submitted to the Coordinating Center who will submit report to Genentech, Inc. if study treatment is Lucentis. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to a study treatment should be reported as an SAE.

8.4.7. Product complaints

A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial. Clinical centers are required to report product complaints for study treatments to the CC on an Unanticpated Event (UA) form within 7 days of learning of the event.

A recent FDA update to the Post Marketing Safety Reporting (PMSR) regulation requires the Marketing Authorization Holder (MAH) to report product complaints to the FDA. Genentech, the

MAH for ranibizumab (Lucentis), is donating the ranibizumab for U.S. clinical centers for the MERIT Trial. As part of the CC's agreement with Genentech, the CC will report any product complaints for ranibizumab reported for the MERIT Trial. The CC will report complaints to Genentech within 15 days

8.4.8. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior exposure to study treatment. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

8.4.9. Reconciliation

The Coordinating Center (the sponsor) agrees to conduct reconciliation for the product donated by Genentech (i.e., Lucentis). The Coordinating Center will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Coordinating Center and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

8.4.10. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

The Lucentis Events of Special Interest are:

- Retinal pigment epithelial tear
- Increased intraocular pressure to > 30mm Hg not responsive to maximal topical IOP-lowering drugs measured on 2 separate days
- Traumatic cataract
- Endophthalmitis
- Intraocular inflammation of greater than 2+ cells (including vitritis and uveitis)
- Retinal detachment
- ATEs, including stroke

8.4.11. SAE Reporting

Investigators must report all SAEs to the Coordinating Center who will report events as applicable to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

- Relevant follow-up information should be submitted to the Coordinating Center who will submit to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the Lucentis and AEs of Special Interest (regardless of causality) will be transmitted to the Coordinating Center within three (3) calendar days of the Awareness Date, The Coordinating Center will transmit Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the Lucentis will be transmitted to the Coordinating Center within three (3) days of the Awareness Date. The Coordinating

Center will submit these reports to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with the Lucentis will be transmitted to the Coordinating Center within seven (7) days of the Awareness date. The Coordinating Center will submit the report to Genentech within thirty (30) calendar days of the Awareness Date.
- The Coordinating Center will forward all Non-serious Adverse Events originating from the Study in a quarterly report or a final listing with the final safety report (FSR) to Genentech.

Note: Investigators should also report events to their IRB as required.

8.4.12. CC event reporting to Genentech

The CC will report all protocol-defined AEs, SAEs, AE of special interest, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE for participants randomizied to or who received ranibizumab during the trial to Genentech by fax: 650-238-6067' or email: usds_aereporting-d@gene.com.

The CC will report ranibizumabl Product Complaints without an AE to Genentech by email: kaiseraugst.global_impcomplaint_management@roche.com

8.5. MedWatch 3500A Reporting Guidelines

The Coordinating Center is responsible for the following.

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information
Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding

SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

8.6. Additional Reporting Requirements for IND Holders

The Coordinating Center holds the IND for MERIT and is responsible for the following.

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of a study treatment. An unexpected adverse event is one that is not already described in the study treatment Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of a study treatment. An unexpected adverse event is one that is not already described in the study treatment investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:
Fax: (650) 225-4682 or (650) 225-5288

And to the Site IRB

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-5288

IND Annual Reports
Copies to Genentech:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

8.7. Study Close-Out

The Coordinating Center is responsible for the following.

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to

Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:
E-mail: lucentisgsr_coa-d@gene.com
Fax: 866-728-4622

9. Sample size and statistical methods

9.1. Sample size, power and detectable differences

The study is powered to test whether intravitreal methotrexate and ranibizumab are each superior to intravitreal dexamethasone in terms of change in central subfield thickness. A Bonferroni correction is used to adjust for the co-primary hypotheses, i.e. a two-sided type I error rate of 0.05/2 = 0.025 will be used to determine statistical significance. The primary outcome, retinal thickness, is measured on the log-scale, which translates to an assessment of relative change compared to baseline. The expected percent reduction in retinal thickness from baseline for dexamethasone is 25% (log [0.75] = -0.2877); macular edema that persists after corticosteroid treatment is expected to be less likely to benefit from additional corticosteroid therapy. We expect the novel treatment arms to produce a reduction of 38% (log [0.62] = -0.4780). A sample size of 79 independent eyes per treatment group, i.e. 79 individuals with one eye for each individual, will provide 91% power to demonstrate an improvement in the percent reduction in retinal thickness from 25% to 38% with a two-sided type I error rate of 0.025. Assuming a between-eye correlation of 0.4, 25% bilateral disease, and a 10% loss to follow-up, we need to enroll 80 individuals in each treatment arm (240 total), 8 fewer participants per arm than would be required if only one eye was included for individuals with bilateral disease after adjusting for loss to follow-up.

We also will compare the percent change in retinal thickness for intravitreal injections of methotrexate and ranibizumab; however, the percent change is expected to be similar for these therapies and the study is not powered to detect equivalence. The calculation presented here is meant to demonstrate the type of difference that would be detectable with the sample required for the primary hypotheses. As noted above, we assume that the reference group will have a percent reduction of 38% (log [0.62]) with a standard deviation for the change in log-retinal thickness of 0.33. A sample size of 79 independent eyes per treatment group (the equivalent of 80 individuals per arm assuming 10% loss to follow-up, 25% bilateral disease and between-eye correlation of 0.4) provides 80% power to detect a difference between the reference percent change of 38% and a percent change of 46.6% (log [0.534]) with a two-sided type I error rate of 0.05.

9.2. Statistical methods

The primary outcome variable is change in log retinal thickness at 12 weeks. A linear regression model fitted with generalized estimating equations[132] will be used to compare the change in log retinal thickness between each of intravitreal methotrexate and ranibizumab with dexamethosone. The mean structure will include treatment effects, a time indicator for weeks 4, 8, 12, 16, 20, and 24, and time-by-treatment interaction terms. The interaction term for 12 weeks represents the difference in change in log retinal thickness from baseline. An unstructured or Toeplitz covariance matrix will be used to model the longitudinal, within-eye repeated measures and the bootstrap will be used to adjust the standard errors to account for the between-eye correlation. Other continuous and binary outcomes will be modeled in a similar manner using linear and logistic models, respectively. In addition, the models will be adjusted for the stratification variable used during randomization (presence or absence of concomitant systemic corticosteroid and/or immunosuppressive therapy).

Kaplan Meier curves will be plotted to graphically portray the cumulative percent with improvement of ME based on OCT central subfield assessment over time for the three treatments. Cox proportional hazards models taking into account the correlation between eyes

through a random effect (also known as a frailty model) will be used to compare the time to improvement of ME for the three treatment arms. Additional time-to-event outcomes (e.g. time to resolution, failure, and relapse) will be analyzed in a similar manner.

The rates of adverse events will be compared using a Negative Binomial model with a random effect for individual. The overall burden and timing of serious adverse events will be displayed graphically by plotting a single line for each individual highlighting the start and stop dates of SAE sorted by the time of first event[133]. Robust standard errors will be computed for all analyses using statistical program-based approaches or the bootstrap, where the unit of analysis is the individual. In addition, the models will be adjusted for the stratification variable used during randomization (presence or absence of concomitant systemic corticosteroid and/or immunosuppressive therapy). All primary analyses will be according to treatment assignment (i.e. following the principles of Intention to Treat). A sensitivity analysis of based upon treatment received will be performed for comparison. Additional sensitivity analyses will be performed to assess the impact of missing data. These include 'best' and 'worst' case single imputations as well as multiple imputation and pattern mixture approaches[134, 135].

10. Efficacy monitoring and stopping guidelines

The guidelines for the interim efficacy analyses were developed by the Data and Safety Monitoring Committee (DSMC) and MUST Executive Committee. Additional unplanned efficacy analyses will be done if recommended by the DSMC or MUST Executive Committee.

A single pre-planned interim efficacy analysis will be performed once 40% of participants have completed the 12-week visit (the primary outcome time-point). The type I error for each of the co-primary comparisons is 0.025, i.e. half was allocated to each comparison to control the study wide type I error rate. For each comparison, the type I error thresholds would be 0.00016 at the interim analysis and 0.02484 at the final analysis to maintain a global 0.025 error rate over the course of the trial based upon O'brien-Fleming boundaries.

11. Regulatory and ethical issues

11.1. Recruitment and informed consent procedures

Eligible patients will be recruited from the patient populations seen at and referred to the MUST Research Group clinical centers located in the United States, United Kingdom, Australia, Canada, and India.. Typically, patients will be identified in the course of usual clinical practice by the study physicians. When a potentially eligible patient is identified, the study physician and study coordinator will describe the study to and discuss the study with the patient. Patients considering enrollment will be given the consent statement and, if applicable, IRB-approved informational materials and be allowed time to decide about joining the study. After patients have time to review materials and discuss enrollment with family members when appropriate, the clinic coordinator or study physician will obtain written informed consent, using a written, local IRB-approved consent document based on a prototype prepared by the CC and approved by the CC's IRB, the JHSPH IRB Office. The trial will be registered on www.ClinicalTrials.gov. Recruitment efforts and eligibility criteria for MERIT are subject to review and approval by IRBs and the DSMC.

11.2. IRB/Protection of human subjects

Potential risks and procedures to minimize risks to participants

The injection procedures, dosage of medication and treatment algorithm within the study will be consistent with standard clinical treatment, e.g., sterile technique, prophylactic pressure lowering medicine instilled prior to procedure. To minimize risks associated with increased ocular pressure post-injection, patients with uncontrolled ocular hypertension or glaucomatous changes will be excluded from the trial. Patients in the trial will not be exposed to risk beyond what they would be exposed to with standard clinical care for their condition. Adverse events encountered will be managed by the best medical judgment of the treating physician.

Confidentiality

Confidentiality of patient data will be maintained in accordance with legal regulations. Protected health information will be kept in a secure place. Name, social security number, address, and other such personal data will be kept solely at the clinical center where the patient receives her/his clinical care. Such information will not be transmitted to the Coordinating Center or to other study sites. A dataset limited so as to contain a minimal amount of protected health information–that required to make the data useful for accomplishing the purposes of the MUST Trial–may be disclosed, as needed, to collaborating study sites, the NEI, and the FDA, as will be stated on a study privacy acknowledgment form signed by the participant at the time of enrollment. Also included in the privacy acknowledgment is the statement that representatives of NEI, FDA, the Institutional Review Boards, and Coordinating Center may see identifying information while reviewing study records. This privacy acknowledgment will be designed to conform to specifications of HIPAA regulations, and any other relevant regulations, as approved by the local governing authorities invested with oversight of HIPAA regulations at each participating site. Clinically relevant information from the study may be placed in the patient's medical record. Release of protected health information to any other persons or organizations will require additional written consent of the patient affected, except as required by law.

Inclusion of children
Patients under 18 years of age will not be included as neither ranibizumab nor the dexamethasone pellet is approved for pediatric use.

Data and safety monitoring
Trial monitoring will be conducted by a study Data and Safety Monitoring Committee (DSMC). The DSMC consists mostly of members of the standing DSMC which monitored the Multicenter Uveitis Steroid Treatment (MUST) Trial and now is monitoring the MUST Follow-up Study. The Chair of the MUST DSMC, who is a biostatistician, is unable to serve because of potential conflicts of interest. Hence a new member who is an experienced methodologist for ophthalmic studies was appointed and the Chair of the DSMC for this protocol is one of the clinical experts. The committee consists of voting members with expertise in biostatistics, clinical trial design, and ophthalmology who were appointed by NEI and non-voting members (i.e., Study Officers).

For each DSMC meeting, data will be summarized by personnel from the CC and presented to the DSMC. The DSMC will meet at least twice a year (one in-person meeting and one meeting by conference call). Additional meetings/conference calls may be requested by DSMC Chair and/or NEI Project Officer. Meeting reports will include information summaries related to monitoring the safety and effectiveness of the study treatments as well as study performance including data quality and clinic performance. Pertinent information from outside sources such as a reprint of a recent publication reporting on results of other, related studies will also be included as available. All reports will include tables and graphs that summarize and formally compare baseline and adverse event data by treatment assignment, and if indicated, within specific subgroups. A single interim efficacy analysis formally comparing the treatment groups will be performed once 50% of participants have completed the 12-week visit (See Section 10). Graphical and/or numeric summaries (without formal statistical comparisons) will be provided in the meeting books that are not associated with the interim efficacy analysis. Additional efficacy analyses may be performed at the request of the DSMC if necessary.

The DSMC Medical Safety Officer, appointed from among the physician voting members of the DSMC, will review all SAE reports received by the CC as described in section 5.1.

12. References

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