NCT Number: NCT03869684

Protocol Number: MT-0814/2-01

Study Title:
A Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of MT-0814 for the Treatment of Patients with Age-Related Macular Degeneration

Protocol Version: Version 4.0: 29 November 2019

CLINICAL STUDY PROTOCOL

[redacted]

A Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of MT-0814 for the Treatment of Patients with Age-Related Macular Degeneration

PROTOCOL NO.: MT-0814/2-01

Sponsor:	Senju Pharmaceutical Co., Ltd. 3-1-9, Kawaramachi, Chuo-Ku, Osaka 541-0048, Japan
Sponsor Contact:	[redacted]
Version of Protocol:	3.0
Date of Protocol:	Original — 16 October 2018 Amendment 1 (v2.0) — 22 January 2019 Amendment 2 (v3.0) — 27 June 2019 Amendment 3 (v4.0) — 29 November 2019

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6: Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of MT-0814 for the Treatment of Patients with Age-Related Macular Degeneration
Protocol Number	MT-0814/2-01
Protocol Date	Protocol Version 4.0 (Incorporating Amendment 3) — 29 November 2019

Protocol accepted and approved by:

[redacted]

Signature

Date

Protocol Approval – Principal/Coordinating Investigator

Study Title	A Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of MT-0814 for the Treatment of Patients with Age-Related Macular Degeneration
Protocol Number	MT-0814/2-01
Protocol Date	Protocol Version 4.0 (Incorporating Amendment 3) — 29 November 2019

Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

Signature _____ Date _____

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of MT-0814 for the Treatment of Patients with Age-Related Macular Degeneration" and the accompanying Investigator's Brochure, Version 3.0, dated 27 June 2019.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 4.0, dated 29 November 2019, the International Council for Harmonisation harmonised tripartite guideline E6: Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Senju Pharmaceutical Co., Ltd., nor will I implement protocol changes without independent ethics committee approval, except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study report or publication.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Senju Pharmaceutical Co., Ltd.

_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

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Protocol Amendment History and Summary of Changes

Version Number	Approval Date	Summary of Changes
1.0	16 Oct 2018	Original Protocol
2.0	22 Jan 2019	Amendment 1 Summary of Significant Changes and Rationale for Each Change 1. Protocol Approval – Sponsor Signatory Change — The address for Senju's Director of Clinical Development [redacted] was changed. Rationale — Address change. 2. General Comment: Entirety of Protocol Synopsis and Body Change — All references to individuals who are participating in Study MT-0814/2-01 have been changed from "patients" to "subjects." Rationale — Sponsor preference. 3. Protocol Synopsis: Rationale Change — The description of the inherent risks in intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) therapy was revised to include the risk to subjects of acquiring sight-threatening endophthalmitis as a result of the procedure. Rationale — Added per the recommendation of the study's coordinating investigator, [redacted] 4. Protocol Synopsis: Rationale; Effects in Humans (Section 1.2) [redacted] 5. Protocol Synopsis: Subject Population; Ocular Exclusion Criteria (Section 4.1.2.1) Change — The criterion that would have excluded subjects with retinal angiomatous proliferation (RAP) lesions in the study eye from participating in the study was deleted. All subsequent exclusion criteria were re-numbered. Rationale — Removed per the recommendation of the study's coordinating investigator, [redacted]
		6. Protocol Synopsis: Efficacy Assessments; List of Abbreviations; Study Design (Section 3.1; Figure 3–1); Efficacy Assessments: Color Fundus Photography (Section 6.1.4); Schedules of Study Events (Table 13–1)

Version Number	Approval Date	Summary of Changes
		Change — The term "color funduscopy" was changed to "color fundus photography." Rationale — Added per the recommendation of the study's coordinating investigator, [redacted] 7. Inclusion Criterion 10 and Schedules of Study Events (Table 13–1; Footnote #i) Change — A statement of note was added that will allow female subjects with positive pregnancy test results to participate in the study if the investigator suspects the result to be a false-positive. Rationale — Previous experience with studies involving elderly female subjects has demonstrated the occasional occurrence of false-positive pregnancy results in postmenopausal women. 8. Ocular Exclusion Criterion 16 Change — The criterion that excludes subjects who had previously received sub-Tenon injections of corticosteroid therapy into the study eye was revised from "within 12 months prior to Day 1" to "within 90 days prior to Day 1." Rationale — Revised per the recommendation of the study's coordinating investigator, [redacted] 9. Missed Doses (Section 5.5.2) Change — The last sentence of this section ("If a dose is considered missed, it should be marked in the diary as missed.") was deleted. Rationale — Technical oversight. 10. Recording of Prior and Concomitant Medications and Procedures (Section 5.8.1) Change — The section was revised to include "and procedures" to both the section heading and the text. Rationale — Typographical error.
		11. Ophthalmological Assessments (Section 6.2.1) Change — The section was revised to indicate that both slit-lamp biomicroscopy and slit-lamp examination will evaluate the condition of the eyelids, conjunctiva, anterior chamber, cornea, and lens of the eyes. Rationale — Typographical error. 12. Clinical Laboratory Tests (Section 6.2.3): Serum Chemistry Change — The list of serum chemistry parameters was revised to include "total cholesterol" and "C-reactive protein."

Version Number	Approval Date	Summary of Changes
		Rationale — Technical oversight. 13. Clinical Laboratory Tests (Section 6.2.3): Urine Drug Test and Schedules of Study Events (Table 13–1): Urine Drug Test Change — Revised to indicate that urine drug tests will be performed at Screening and on Day 1. Rationale — Typographical error. 14. Statistical and Analytical Plan: Description of Subgroups to be Analyzed (Section 7.6) Change — Revised to include an efficacy subgroup analysis for the presence versus absence of RAP. Rationale — Technical oversight. 15. Statistical and Analytical Plan: Subject Demographics and Other Baseline Characteristics (Section 7.7) and Treatment Exposure and Compliance (Section 7.8) Change — Revised to clarify that these analyses will be performed for the full analysis set, the per-protocol set, and the safety set of the study's subjects. Rationale — Technical oversight. 16. Statistical and Analytical Plan: Clinical Laboratory Tests (Section 7.9.4.4); Schedules of Study Events (Table 13–1): Serum Chemistry Change — Revised to include serum chemistry tests and analyses at Week 4 and Week 8. Rationale — Revised per United States Food and Drug Administration (FDA) non-hold comments for Investigational New Drug [redacted]
		17. Schedules of Study Events (Table 13–1): Physical Exam, Medical/Medication History Change — Revised to include this event on Day 1. Rationale — Typographical error. 18. Schedule of Study Events (Table 13–1) Change — Three additional rows were added to the end of the table, indicating the following events on the study schedule: "study drug dispensed," "concomitant medications reviewed," and "subject diary reviewed." Rationale — Technical oversight.
3.0	27 June 2019	Amendment 2

Version Number	Approval Date	Summary of Changes
		Summary of Significant Changes and Rationale for Each Change 1. Protocol Synopsis: Subject Population; Inclusion Criteria (Section 4.1.1) Change — Inclusion criterion 3 was updated to include specification on the choroidal neovascularization (CNV). The criterion was updated as follows: Has active CNV (classic and/or occult), either subfoveal or juxtafoveal (<200 µm from central fovea), associated with AMD, as evidenced on fluorescein angiography and/or indocyanine green angiography at Screening (at which the assessment will be performed by a single central reading facility). Change — Inclusion criterion 5 was updated to include the Screening assessment time point for eligibility consideration. The revised criterion is as follows: Has an Early Treatment Diabetic Retinopathy Study best-corrected visual acuity score of 24 to 78 letters for the study eye at Screening and on Day 1. Rationale — Added per the administrative clarification received for the protocol dated 25 February 2019. 2. Protocol Synopsis: Subject Population; Exclusion Criteria (Section 4.1.2.1) Change — Exclusion criterion 15 was updated to include example of photodynamic therapy (such as Vsudyne®)". This criterion was also added in the protocol synopsis Subject Population section as it was not previously added. Rationale — The example of photodynamic therapy was added to be consistent with the changes made in the Prohibited Concomitant Medications, Treatments, and Procedures (Section 5.8.2). 3. Protocol Synopsis: Study Design; Study Design (Section 3.1); Treatments Administered (Section 5.2); Treatment Compliance (Section 5.7); Schedules of Study Events (Table 13–1): Study Drug Administration Change — Added clarification that on the day of End of Treatment, only the morning (ie, AM) dose of the study drug should be taken by subjects. For the Schedules of Study Events, (Table 13–1), a footnote "j" was added to clarify that that on the day of End of Treatment, only the morning (ie, AM) dose of the study drug should be taken. Rationale — Added per the administrative clarification received for the protocol dated 09 May 2019. [redacted]

Version Number	Approval Date	Summary of Changes
		[redacted]  5. Color Fundus Photography (Section 6.1.4) Change — Added that the color fundus photography assessment was also regarded as a safety assessment. In addition, added the following sentence on the overall time points (ie, Screening and after Screening) when the items with color fundus photography will be assessed. Rationale — Added per the administrative clarification received for the protocol dated 25 February 2019. 6. Reporting Adverse Events (Section 6.2.2.3) Change — Replaced the terms “eye” and “face [except eyes]” with “ocular” and “non-ocular”, respectively, when describing the location of event. Rationale — [redacted] The term “face [except eyes]” is deleted because it is not necessary to collect adverse events in the face separately. In the electronic case report form (eCRF), the site or location of the event is designated as “ocular” or “non-ocular”. Therefore, to accord with the eCRF, the term “eye” in the protocol were updated. 

Version Number	Approval Date	Summary of Changes
		[redacted] 8. Minor corrections and Clarifications Change — The amendment also includes some other minor clarifications and corrections. Rationale — Minor corrections and clarifications are included in the revised text for consistency.
4.0	06 Dec 2019	Amendment 3
		Summary of Significant Changes and Rationale for Each Change
		1. Protocol Synopsis: Subject Population; Ocular Exclusion Criterion 14 (Section 4.1.2.1) Change — The criterion that excludes subjects who had a medical history of any anti-VEGF treatment via intravitreal injection "for either eye" was revised to "the study eye." A note for the fellow eye was also included "Subjects who are planning to receive an anti-VEGF injection into the fellow eye during the study period will be excluded." Rationale — Revised to consider the inclusion of subjects with previously diagnosed and treated wet AMD in the fellow eye, and who have developed wet AMD in their study eye and who have received anti-VEGF in the fellow eye.
		2. Masking: Breaking the Mask (Section 5.6.1) Change — Added that unmasked subject data will be available to specific designated Senju personnel only; the mask will be maintained for all other Senju and PPD operational team members, as well as investigators and subjects. Rationale — Text was added to indicate that unmasked subject data will be available to select individuals at Senju and not to other members at Senju and PPD.
		3. Prior and Concomitant Therapy: Recording of Prior and Concomitant Medications and Procedures (Section 5.8.1) Change — Added text on recording the date of the last dose of anti-VEGF treatment in the fellow eye. Rationale — Revised to include the recording of prior anti-VEGF treatment in the fellow eye. 4. Prohibited Concomitant Medications, Treatments and Procedures (Section 5.8.2)

Version Number	Approval Date	Summary of Changes
		Change — The prohibited use of anti-VEGF agents (systemic use or administered via intravitreal injection was revised from "either eye" to "the study eye." A note for the fellow eye was also included "Injection of anti-VEGF into the fellow eye during the study period is prohibited. If the subject requires anti-VEGF treatment in the fellow eye, the subject should be discontinued from the study, and the EOT assessments should be completed. Rationale — Revised to discontinue subjects who have received anti-VEGF in the study eye and fellow eye (during the study).
		5. Statistical and Analytical Plan: Analysis of Primary Efficacy Endpoint (Section 7.9.1) Change — Modified the statistical method by replacing "MMRM" with "ANCOVA" for sensitivity analysis at Week 12 incorporating data from the fellow eye with missing data at Week 12 imputed using WOCF. Rationale — Revised as the analysis could not be performed using the MMRM model with this data structure.
		6. Safety Analyses: Schedules of Study Events (Table 13–1): Serum Chemistry Change — Revised to include the collection of additional serum chemistry samples at Weeks 0, 1, 2, 3, 5, 6, 7, 9, 10, and 11. Rationale — Revised per safety review committee meeting discussion. 7. Slit-Lamp Biomicroscopy (Section 7.9.4.6) Change — Revised to exclude lens opacity assessments obtained via LOCS III for ocular findings. Rationale — Revised as lens opacity assessments will not be evaluated using normal/abnormal categories.
		8. Minor corrections and clarifications Change — The amendment also includes additional minor clarifications and corrections. Rationale — Minor corrections and clarifications are included in the revised text for consistency.

Protocol Synopsis

Protocol Number: MT-0814/2-01

Title: A Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of MT-0814 for the Treatment of Patients with Age-Related Macular Degeneration

Sponsor: Senju Pharmaceutical Co., Ltd.
3-1-9, Kawaramachi, Chuo-Ku, Osaka 541-0048, Japan

Study Phase: Phase 2a

Study Sites: Approximately 15 sites in the United States

Indication: Exudative (wet) age-related macular degeneration (AMD)

Rationale: Age-related macular degeneration is the leading cause of blindness among adults in North America, and the fourth-leading cause of visual disorders in Japan. The current standard of care for patients with exudative ("wet") AMD is anti-vascular endothelial growth factor (anti-VEGF) therapy, which must be administered via intravitreal injection every 4 to 8 weeks. Such therapy exposes patients to the risk of acquiring sight-threatening endophthalmitis, increases patient susceptibility to infections, and places a severe burden on both patients and caregivers. [redacted]

Objectives: This study is being conducted to evaluate the safety, tolerability, efficacy, and PK of [redacted] MT-0814 administration versus placebo in subjects with AMD.

Subject Population: Male and female subjects 50 years of age or older with AMD, classic and/or occult CNV, either subfoveal or juxtafoveal (<200 µm from central fovea), associated with AMD at Screening, and a best-corrected visual acuity (BCVA) score (obtained via the Early Treatment for Diabetic Retinopathy Study [ETDRS]) of 24 to 78 letters at Screening and on Day 1 will be eligible to participate in the study. Subjects must also have a "study eye" with a total lesion area <30.5 mm^2 (of which ≥50% of the total lesion area must be CNV area) and retinal fluid accumulation; nevertheless, the study eye must have a clear optic media that is conducive to high-quality fundus imaging.

Subject Population (continued):

Subjects with any of the following will be excluded: active CNV due to causes other than AMD; BCVA <34 letters in the fellow eye; myopia greater than -8 diopters in the study eye; fibrosis and/or geographic atrophy of the foveal center of the study eye; retinal pigment epithelial tears and/or rips in the study eye; retinal vascular disease or retinal degeneration in the study eye due to causes other than AMD; subretinal hemorrhaging in the study eye occupying ≥50% of the total lesion area; vitreous hemorrhaging in the study eye; intraocular surgery, cataract surgery, or LASIK surgery on the study eye within 90 days prior to Day 1, or yttrium aluminum garnet laser capsulotomy on the study eye within 30 days prior to Day 1; any active inflammation, infection, or other severe ocular disease in either eye, or aphakia in the study eye; uncontrolled glaucoma or history of previous glaucoma filter surgery in either eye; previous treatment with anti-VEGF via intravitreal injection in the study eye; history of photodynamic therapy (such as Vsudyne®), laser photocoagulation, radiation therapy, vitrectomy, and/or other surgical intervention for the treatment of AMD for the study eye; history of corticosteroid treatment via intravitreal injection into the study eye within 12 months prior to Day 1 or via sub-Tenon or subconjunctival injection into the study eye within 90 days prior to Day 1; history of intravitreal implants of corticosteroids fluocinolone acetonide or dexamethasone; contact lens wearer who is unable to discontinue their use in both eyes; treatment with any topical and/or systemic corticosteroid within 28 days prior to Day 1; treatment with any systemic anti-VEGF within 90 days prior to Day 1; unsatisfactory kidney or liver function; serious allergy or prior significant adverse reaction to fluorescein or indocyanine green; undiagnosed acute illness, clinically meaningful active gastrointestinal disease, or severe concurrent medical condition at Screening or Baseline; history or evidence of alcohol or drug abuse within 180 days prior to Day 1.

Study Design:

This is a double-masked, randomized, multicenter, placebo-controlled, parallel-group study in adult subjects with exudative AMD. Subjects will be randomly assigned in a 3:3:1 allocation ratio to receive MT-0814 [redacted], MT-0814 [redacted], or placebo [redacted] for 12 weeks, [redacted] followed by a 4-week follow-up period in which study drug will not be administered. Randomization will be stratified by Baseline BCVA score category (BCVA scores of ≤55, 56 to 70, or ≥71) of the study eye on Day 1.

Estimated Study Duration:

This study is planned to last up to 18 weeks, including a screening/washout period of approximately 2 weeks, a 12-week treatment period, and a 4-week follow-up period where study drug will not be administered. There will be a total of 18 study visits.

Efficacy Assessments:

The primary efficacy measure is the assessment of change from Baseline in BCVA (via the ETDRS) at Week 12. The key secondary efficacy measure is the assessment of change (from Baseline) in the central subfield thickness (CSFT) at Week 12.

Additional efficacy measures include the following: changes from Baseline at each visit in CSFT, optical coherence tomography parameters, total lesion area (measured by fluorescein angiography [FA], indocyanine green angiography [ICGA], and color fundus photography [CFP]), CNV area (measured by FA, ICGA, and CFP), leakage area (measured by FA, ICGA, and CFP), regression of polypoidal choroidal vasculopathy, percentages of subjects requiring anti-VEGF rescue therapy; proportions of subjects who achieve dry retina at Weeks 4, 8, 12, and 16; and duration from start of treatment to the time that anti-VEGF rescue therapy is initiated.

Safety Assessments:

Safety assessments include monitoring of AEs, ophthalmological assessments (visual acuity, FA/ICGA, CFP, slit-lamp biomicroscopy examination, and measurement of intraocular pressure, physical examination findings, vital sign measurements, electrocardiogram findings, clinical laboratory tests, and monitoring of concomitant medications.

MT-0814 Plasma Concentration Assessments:

Predose and postdose plasma concentrations of MT-0814 and its metabolites M5 and M6 will be assessed on Days 1, 29, 57, and 85 of the study.

Study Drug, Dosage, and Route of Administration:

Subjects will be randomly assigned in a 3:3:1 ratio to receive one of the following:

- MT-0814 [redacted] for 12 weeks, or
- MT-0814 [redacted] for 12 weeks, or
- Placebo [redacted] for 12 weeks

[redacted]

Sample Size:

Approximately 35 subjects are planned to be enrolled.

Statistical Methods:

Efficacy Analyses

Primary Endpoint

The primary endpoint is the assessment of change from Baseline in BCVA (via ETDRS) at Week 12. A 2-sided hypothesis will be tested: whether the change from Baseline to Week 12 in BCVA between MT-0814 and placebo are equal or not equal. The primary analysis will be performed using an analysis of covariance (ANCOVA) model including fixed effect for treatment and Baseline BCVA score as a covariate. Subjects with missing data at Week 12 or who receive rescue therapy will have their data imputed by worst observation carried forward method. Only postbaseline observations observed prior to dropout or receipt of rescue therapy (whichever occurs first) will be carried forward. Additional sensitivity analyses may be performed.

Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the assessment of change (from Baseline) in the CSFT at Week 12. Analysis will be performed using an ANCOVA model including fixed effect for treatment and Baseline CSFT score as a covariate. Selected sensitivity analyses (like those identified for the primary efficacy endpoint) may also be performed. Analysis will be performed separately to compare each dose of MT-0814 to placebo (eg, including only subjects receiving placebo and subjects receiving the MT-0814 dose being compared to placebo.).

Other Secondary Efficacy Endpoints

Endpoints for changes from Baseline at each visit will be analyzed using an ANCOVA model applying treatment as fixed effect and the parameter's Baseline value as the covariate. The t-tests will also be performed for changes from Baseline. Endpoints for proportions of subjects will be analyzed using Fisher's Exact test. Kaplan-Meier estimates will be presented for the time to receipt of rescue therapy.

Analyses will be performed separately to compare each dose of MT-0814 to placebo (eg, including only subjects receiving placebo and subjects receiving the MT-0814 dose being compared to placebo).

Statistical Methods (continued):

Safety Analyses

Safety data will be summarized and listed with no statistical hypothesis testing performed. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

Date of Protocol: 29 November 2019 (Version 4.0, incorporating Amendment 3)

List of Abbreviations

Abbreviation	Definition
AE	adverse event
$Ae\%_{0\text{-}72h}$	urinary excretion ratio of drug from zero up to 72 hours
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero extrapolated to infinity
BCVA	best-corrected visual acuity
[redacted]	[redacted]
BSL	Baseline
[redacted]	[redacted]
[redacted]	[redacted]
CFP	color fundus photography
CFR	Code of Federal Regulations
CL_R	clearance rate
C_{max}	maximum plasma concentration
CNV	choroidal neovascularization
CSFT	central subfield thickness
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of (the) study [Defined as Week 16/Visit 18 or the final visit at which the subject is permanently discontinued/withdrawn from participation in the study.]
EOT	end of treatment [Defined as Week 12/Visit 14 or the final visit at which the subject is permanently discontinued/withdrawn from study drug administration.]
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	full analysis set
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICGA	indocyanine green angiography
ICH	International Council for Harmonisation
IOP	intraocular pressure

Abbreviation	Definition
IRB	institutional review board
IWRS	interactive web response system
LOCS III	Lens Opacities Classification System III
MCP	monocyte chemo-attractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed models repeated measures (analysis)
[redacted]	[redacted]
[redacted]	[redacted]
OCT	optical coherence tomography
OTC	over-the-counter
PCV	polypoidal choroidal vasculopathy
PK	pharmacokinetics
[redacted]	[redacted]
PPD	Pharmaceutical Product Development
PPS	per-protocol set
PT	preferred term
RAN	randomization
[redacted]	[redacted]
RAP	retinal angiomatous proliferation
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOE	schedule of events
SOT	start of (the) treatment
SS	safety set
$T_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time of maximum plasma concentration
[redacted]	[redacted]
US	United States
VEGF	vascular endothelial growth factor
WOCF	worst observation carried forward
YAG	yttrium aluminum garnet

1 Introduction

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3 Rationale for Phase 2a Study MT-0814/2-01

Age-related macular degeneration is the leading cause of blindness among adults in North America and Europe,[5,6] and it is the fourth-leading cause of visual disorders in Japan.[7] Moreover, the prevalence of AMD has increased in recent years, and its incidence is expected to increase further due the continued aging of the world population.[8] In exudative (wet) AMD, CNV formation is induced by the secretion of vascular endothelial growth factor (VEGF), leading to a rapid decrease in visual acuity due to retinal edema and/or bleeding.[9,10]

The current standard of care for patients with exudative AMD is the administration of anti-VEGF agents (aflibercept or ranibizumab) via an intravitreal injection every 4 to 8 weeks.[11,12] Treatment with anti-VEGFs has been demonstrated to benefit patients with AMD by maintaining or even improving visual acuity.[13,14,15] However, lifetime dosing of anti-VEGF every 1 to 2 months exposes patients to the risk of acquiring infectious diseases from the intravitreal injection procedure. Additionally, the intravitreal injection procedure itself places a severe burden on patients, caregivers, and ophthalmologists. [redacted]

As MT-0814 is an investigational drug with a limited safety profile in humans, all subjects receiving MT-0814 will be closely monitored until sufficient exposure in humans is obtained to determine the clinical safety of MT-0814.

1.4 Risk-Benefit Assessment

Any potential risks associated with MT-0814 are considered low, based on results obtained from animal model repeat-dose toxicity studies, as the no observed adverse effect level for MT-0814 for both male and female animals [redacted]

[redacted] Please refer to the Investigator's Brochure for detailed information concerning the available nonclinical and clinical information of MT-0814.

2 Study Objectives

2.1 Primary Objectives

The primary objective of this study is to assess the safety, tolerability, efficacy, and PK of [redacted] MT-0814 administration versus placebo in subjects with AMD.

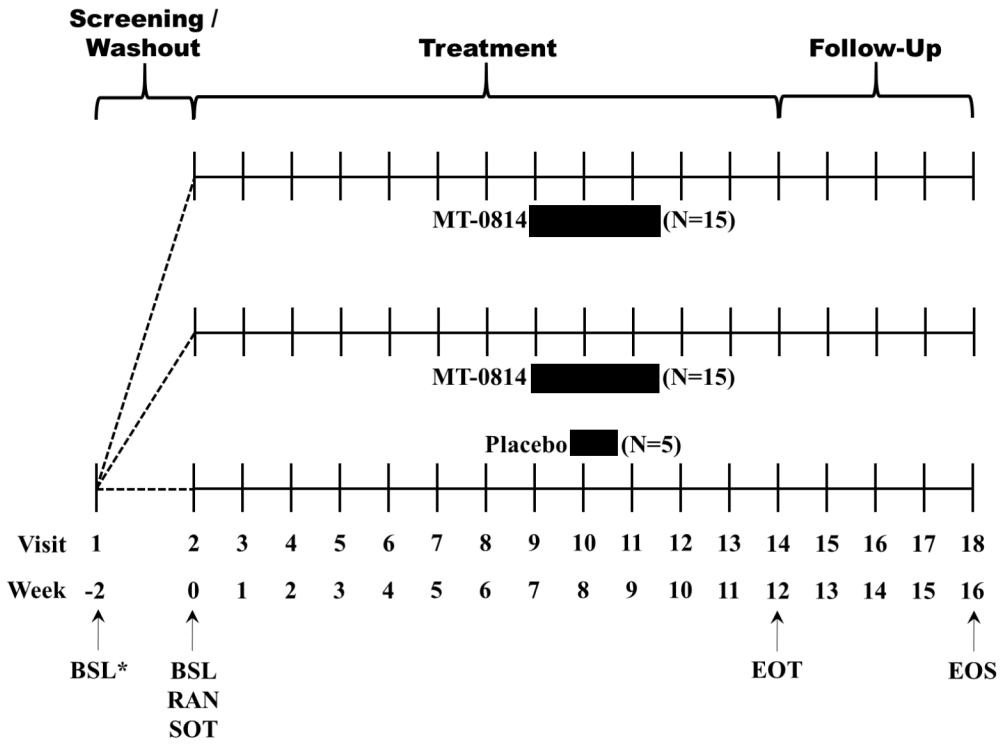
3 Investigational Plan

3.1 Study Design

This is a double-masked, randomized, multicenter, placebo-controlled, parallel-group study in adult subjects with exudative AMD. Subjects will be randomly assigned in a 3:3:1 allocation ratio to receive MT-0814 [redacted], MT-0814 [redacted], or placebo [redacted] for 12 weeks, [redacted] followed by a 4-week follow-up period. Randomization will be stratified by the BCVA score category (BCVA scores of ≤55, 56 to 70, or ≥71) observed for the subject's study eye on Day 1 (Baseline).

This study is planned to last up to 18 weeks (with 18 study visits), including a screening/washout period of ≤14 days (≤2 weeks), a 12-week treatment period, and a 4-week follow-up period in which study drug will not be administered (Figure 3–1).

Figure 3–1 Study Design: Study Periods and Visit Schedule



Abbreviations: [redacted] BSL = Baseline; EOS = end of study; EOT = end of treatment; RAN = randomization; SOT = start of treatment.
* Baseline assessments for fluorescein angiography, indocyanine green angiography, and color fundus photography will be collected at Screening (Visit 1) instead of Visit 2.

For subjects who used prohibited concomitant medications within 14 days prior to the planned randomization date, a washout period will be required prior to the first dose of study drug. The duration of this washout must be a minimum of 14 days for any prohibited ocular, nasal, and systemic medications (defined as those delivered by injection, oral, or transdermal methods) prior to the planned randomization date.

Approximately 35 subjects will be enrolled in the study. Once the Screening visit laboratory test results are confirmed, subjects who still meet all inclusion criteria and none of the exclusion criteria will be randomly assigned in a 3:3:1 ratio to receive one of the following treatment regimens:

1. MT-0814 [redacted] for 12 weeks (N=15)
2. MT-0814 [redacted] for 12 weeks (N=15)
3. Placebo [redacted] for 12 weeks (N=5)

[redacted] Following training and under supervision, subjects will receive the first dose of study drug at the study site on Day 1 (Week 0). If a subject withdraws prematurely from the study before the completion of the treatment period (that is, before the Week 12 visit), a final visit must be scheduled for End of Study (EOS) assessments.

Efficacy, safety, and plasma concentration assessments will be performed as presented in the schedule of events (SOE) (Table 13–1); the plasma concentration sample collection schedule is presented in Table 13–2. Efficacy, safety, and plasma concentration measures are listed below.

- The primary efficacy measure is the assessment of change (from Baseline) in BCVA (measured by the Early Treatment of Diabetic Retinopathy Study [ETDRS]) at Week 12.

- The key secondary efficacy measure is the assessment of change (from Baseline) in the CSFT at Week 12.

- Additional efficacy/safety measures include assessment of the changes observed from Baseline at each visit for the following:

- Best-corrected visual acuity
- Central subfield thickness
- Optical coherence tomography (OCT) parameters
- Total lesion area (as measured by fluorescein angiography [FA], indocyanine green angiography [ICGA], and color fundus photography [CFP])
- Choroidal neovascularization area (as measured by FA, ICGA, and CFP)
- Leakage area (as measured by FA, ICGA, and CFP)
- Regression of polypoidal choroidal vasculopathy (PCV)
- Proportions of subjects requiring anti-VEGF rescue therapy

- Proportions of subjects who achieve dry retina (defined as an absence of visible intraretinal cystoid edema or subretinal fluid on OCT scan) at Weeks 4, 8, 12 (EOT), and 16 (EOS).
- Duration from start of treatment (SOT) to the time that anti-VEGF rescue therapy is initiated.
- Other safety measures include monitoring of AEs, ophthalmological assessments (visual acuity, FA/ICGA, CFP, slit-lamp biomicroscopy examinations, and measurement of intraocular pressure [IOP]), physical examination findings, vital sign measurements, ECG findings, clinical laboratory tests, and monitoring of concomitant medications.
- Predose and 2-hour postdose plasma concentrations of MT-0814 and its metabolites M5 and M6 on Days 1, 29, 57, and 85 of the study.

3.1.1 Rationale for Study Design

This Phase 2a study has a double-masked, randomized, multicenter, placebo-controlled, parallel-group design. The study will evaluate the safety, tolerability, efficacy, and PK of [redacted] MT-0814 administration for the treatment of subjects with AMD. [redacted] given this fact, and given that this is a small, proof-of-concept study to detect whether MT-0814 is effective against the signs and symptoms of AMD, it is considered appropriate to compare the study

drug against a placebo. Subjects who participate in this study will be examined on a weekly basis, and rescue therapy (via anti-VEGF injection; refer to Section 4.2.3 for details) will be provided in the event that further disease-related deterioration is observed.

[redacted]

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 35 subjects are planned to be enrolled at approximately 15 sites in the United States (US). Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Ocular inclusion and exclusion criteria must all be met in the same eye for at least one of the subject's eyes — that eye will be the "study eye." If both eyes meet all inclusion and exclusion criteria, the eye with the lower ETDRS score (that is, the eye in which fewer letters are correctly identified) at Screening will be selected as the study eye. If both eyes meet all entry criteria and have identical ETDRS scores at Screening, selection of the study eye will be at the investigator's discretion.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent form (ICF), provides signed and witnessed written ICF, and agrees to comply with protocol requirements, including all required study visits.
2. Is a male or female 50 years of age or older.
3. Has active CNV (classic and/or occult), either subfoveal or juxtafoveal (<200 μm from central fovea), associated with AMD, as evidenced on FA and/or ICGA at Screening and as assessed by a single central reading facility.
4. Has a total CNV area that is ≥50% of the total lesion area in the study eye at Screening as assessed by a single central reading facility.
5. Has an ETDRS BCVA score of 24 to 78 letters for the study eye at Screening and on Day 1.
6. Has a total lesion area <30.5 mm^2 in the study eye at Screening as assessed by a single central reading facility.
7. Has retinal/subretinal fluid in the study eye at Screening (detected by OCT scan) as assessed by a single central reading facility.
8. Has a clear optic media in the study eye that is capable of producing high-quality fundus images.

[redacted]

10. If the subject is a female (either a female of childbearing potential or postmenopausal; both defined below), she must have a negative serum pregnancy test result at Screening (Visit 1). Additionally, female subjects who are premenopausal or have been postmenopausal for <1 year must have a negative urine pregnancy dipstick test result on Day 1 before being randomly assigned to study treatment. Females of childbearing potential must also agree to use effective contraception throughout the study.

    A female of childbearing potential is defined as the following:

    - Has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Women who are already using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or who have a partner that is sterile (eg, vasectomy) should be considered to be of childbearing potential.

    A postmenopausal female is defined as the following:

    - Has had amenorrhea ≥12 consecutive months without another cause and a documented serum follicle-stimulating hormone level >35 mIU/mL
    - Has had irregular menstrual periods and a documented serum follicle-stimulating hormone level >35 mIU/mL, or
    - Has been on hormone replacement therapy

    Note: If a female subject has a positive pregnancy test result (serum and/or urine dipstick) but the investigator suspects that the result is a false-positive, the female subject can participate in the study at the investigator's discretion.

11. If the subject is a male, he must agree to use an acceptable form of contraception (eg, a condom plus spermicide) and must agree to refrain from sperm donation throughout the study.
12. Is otherwise healthy, as determined by physical examination findings at Screening and Day 1.
13. Has a negative urine drug test result at Screening and Day 1.
    - If the investigator has medical evidence to support that the positive urine drug test result is due to a prescribed concomitant medication and not due to drug abuse, an exception can be granted to enroll a subject with a positive urine drug test. The site must appropriately document the decision for this specific scenario in the source documents and electronic case report form (eCRF).

4.1.2 Exclusion Criteria

[Note: For the purposes of this protocol, "systemic" drug/medication use is defined as any medication that may ultimately affect the eye (specifically the retina) and is delivered by injection or oral methods.]

Subjects meeting any of the following criteria will be excluded from the study:

4.1.2.1 Ocular Exclusion Criteria

1. Has active CNV due to causes other than AMD in the study eye at Screening.
2. Has a BCVA score <34 letters (equivalent to a Snellen fraction of 20:200 or worse) in the fellow eye at Screening and/or Day 1.
3. Has myopia greater than -8 diopters in the study eye at Screening and/or Day 1.
4. Has fibrosis and/or geographic atrophy involving the foveal center of the study eye at Screening as assessed by a single central reading facility.
5. Has retinal pigment epithelial tears and/or rips in the study eye at Screening as assessed by a single central reading facility.
6. Has retinal vascular disease or retinal degeneration other than AMD (eg, retinal vein occlusion, diabetic retinopathy, diabetic macular edema, etc.) in the study eye at Screening as assessed by a single central reading facility.
7. Has subretinal hemorrhaging that occupies ≥50% of the total lesion area in the study eye at Screening as assessed by a single central reading facility.
8. Has vitreous hemorrhaging in the study eye at Screening and/or Day 1.
9. Had intraocular surgery, cataract surgery or LASIK surgery on the study eye within 90 days prior to Day 1.
10. Had yttrium aluminum garnet (YAG) laser capsulotomy on the study eye within 30 days prior to Day 1.
11. Has active inflammation, infection, or other severe ocular disease in either eye at Screening and/or Day 1.
12. Has aphakia in the study eye at Screening and/or Day 1.
13. Has uncontrolled glaucoma at Screening and/or Day 1 or has a history of previous glaucoma filter surgery in either eye.
14. Has a medical history of any anti-VEGF (bevacizumab, pegaptanib, ranibizumab, aflibercept, etc.) treatment via intravitreal injection for the study eye.

    Note: Subjects who are planning to receive an anti-VEGF injection into the fellow eye during the study period will be excluded.

15. Has a history of photodynamic therapy (such as Vsudyne®), laser photocoagulation, radiation therapy, vitrectomy, and/or other surgical intervention for the treatment of AMD for the study eye.
16. Has a history of corticosteroid treatment via intravitreal injection into the study eye within 12 months prior to Day 1 or via sub-Tenon or subconjunctival injection into the study eye within 90 days prior to Day 1.
17. Has a history of receiving intravitreal implants of the corticosteroids fluocinolone acetonide (ILUVIEN®) or dexamethasone (OZURDEX®).
18. Is a contact lens wearer and is unable to discontinue their use in both eyes for the entire duration of the study.

4.1.2.2 General Exclusion Criteria

19. Has been treated with any topical and/or systemic corticosteroid agent within 28 days prior to Day 1 (except for topical dermal administration outside the periocular area — refer to Exclusion Criterion 16).
20. Has been treated with any systemic anti-VEGF any within 90 days prior to Day 1.
21. Has unsatisfactory kidney or liver function (as determined from laboratory test results) at Screening.
22. Has a serious allergy to or experienced a prior significant adverse reaction to FA or ICGA.
23. Has an undiagnosed acute illness first observed during Screening or between Screening and Baseline, or has a severe concurrent medical condition that, in the investigator's judgment, represents a safety concern.
24. Has a history of or evidence of alcohol or drug abuse within 180 days prior to Screening.
25. Has participated in any other clinical study and/or has taken any investigational drug or product within 90 days prior to Screening.
26. Has clinically meaningful active gastrointestinal disease as determined by the investigator.
27. Is considered by the investigator to be unable or unlikely to comply with the study protocol or the scheduled visits (eg, planned travel outside of the study area for a substantial portion of the study period, scheduled hospitalization during the study, etc.).
28. Is determined by the investigator to have any other clinically meaningful condition (or history thereof) that may adversely impact the ability of the subject to safely participate in the study or may confound the results that are obtained from the subject during the study.
29. Is an employee or family member of the investigator or study site staff.

4.2 Subject Withdrawal and Replacement

The duration of the study is defined for each subject as the date the signed written ICF is provided through the last visit at Week 16 or through the early withdrawal visit (ie, the EOS visit for subjects who withdraw before the end of the treatment period).

4.2.1 Reasons for Withdrawal/Discontinuation

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any subject withdraws from the study prematurely.

Subject participation may be terminated prior to completing the study and the reason recorded as follows:

1. A serious or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study
2. Noncompliance with the protocol
3. Subject withdraws consent
4. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal
5. Other (eg, pregnancy or development of contraindications of use of study drug)

The investigator will also withdraw a subject if Senju Pharmaceutical Co., Ltd. terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. A genuine effort must be made to determine the reason(s) why a subject is discontinuing from the study.

Compliance with the study drug regimen is crucial for accurate endpoint analysis. Subject compliance will be discussed with the subject by the site staff at each visit, which will include a discussion on barriers to compliance.

4.2.2 Handling of Withdrawals

Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all subjects who permanently discontinue study treatment or withdraw from the study

prematurely will undergo all EOS assessments (for subjects who withdraw before Week 16). Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject requesting that he or she should contact the study site.

All subjects who withdraw from the study with an ongoing AE must be followed until the AE is resolved or deemed stable.

All subjects who withdraw from the study due to pregnancy must be followed to record the outcome of the pregnancy. See Section 6.3 for further information on the procedures for following female subjects who become pregnant during the study.

If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the study site should be collected at the time of premature discontinuation or at the scheduled EOS visit.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures. If study drug is interrupted for a safety reason, it is at the discretion of the investigator whether to continue treatment with the study drug.

4.2.3 Treatment Failure and Initiation of Rescue Therapy

In case the investigator considers that the ocular condition is worsening to an extent that the subject needs rescue medication, the subject will be considered a treatment failure. Investigators should discontinue administration of study drug and begin rescue therapy with intravitreal injections of an anti-VEGF agent (aflibercept or ranibizumab) per standard of care if a subject exhibits any of the following:

- Increase in retinal/subretinal hemorrhage or new retinal/subretinal hemorrhage from Screening for which the investigator deems rescue therapy is necessary.
- Emergence of new retinal/subretinal fluid, increase in retinal/subretinal fluid, or cystoid macular edema from Day 1 for which the investigator deems rescue therapy is necessary.
- Decrease in BCVA of ≥10 letters from Day 1 that is related to disease activity.
- Any other reason that, in the investigator's opinion, requires discontinuation of study drug and initiation of rescue therapy.

All EOT evaluations need to be completed at the time that treatment failure has been declared.

4.2.4 Replacements

Subjects withdrawn prematurely from the study will not be replaced. Study candidates who failed Screening will be permitted to re-screen once at the investigator's discretion.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to receive MT-0814 [redacted] MT-0814 [redacted], or placebo [redacted] using a 3:3:1 allocation ratio. Randomization will be stratified by the BCVA score category (BCVA scores of ≤55, 56 to 70, or ≥71) observed for the subject's study eye on Day 1 (Baseline).

An interactive web response system (IWRS) will be used to administer the randomization schedule. An independent statistician of the sponsor's designated contract research organization, PPD, will generate a permuted block randomization schedule using SAS software Version 9.4 or higher (SAS Institute Inc, Cary, North Carolina) for IWRS, which will link sequential subject randomization numbers to treatment codes. Each subject will be assigned a randomization number that will be separate from the subject identification number. Once a randomization number has been allocated to 1 subject, it may not be assigned to another subject.

5.2 Treatments Administered

[redacted]

5.3 Identity of Investigational Product

The following will be used in the study:

Product	Supplied As	Strength
MT-0814	[redacted]	[redacted]
Placebo (Vehicle)	[redacted]	[redacted]

[redacted]

The manufacturing facility will provide adequate supplies of masked study drug (that is, MT-0814 or placebo) to study sites.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

MT-0814 and matching placebo will be prepared in blister packs and shipped by the manufacturing facility. Study drug will be packaged and labeled according to applicable local and regulatory requirements.

[redacted]

Figure 5–1 [redacted]

A total of 70 individual blister packs of the same MT-0814 dose will be packaged in a box (or kit). A single box (or kit) of study drug will be dispensed to each subject every 4 weeks (Weeks 0, 4, and 8).

All supplies of the study drug must be stored in accordance with the manufacturer's instructions. The storage conditions and expiry date are indicated on the label. MT-0814 has been assigned an expiration of 3 years from the date of packaging when stored at room temperature. The study drug will be stored in a securely locked area, accessible to authorized persons only, until needed for dispensing.

The materials schedule will be prepared by an independent PPD statistician and provided to the IWRS and the packaging vendor. At the time of randomization, the IWRS will assign each subject a study drug kit corresponding to the subject's randomly assigned treatment based on the drug supply inventory that is available at the site. The kit will be identified by a unique kit number that is separate from the subject or randomization numbers. At Week 0 (Day 1), Week 4, and Week 8, the investigator will dispense an assigned treatment kit to the subject.

5.4.2 Test Article Accountability

The sponsor's manufacturing facility will ship a sufficient supply of study drug to each study site directly or from a local depot. The investigator has the responsibility for confirming that all study drug treatment supplies received by the site are inventoried and accounted for throughout the study. A drug receipt log is to be filled out and signed by the person accepting the shipment. It is important that the designated site staff count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.
The investigator must notify the manufacturing facility and PPD of any damaged or unusable study drug kits that were supplied to the investigator's site. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.4.3 Other Supplies

The sponsor will also provide study sites with study drug administration diaries.

5.5 Medication Errors

On Day 1, subjects will be instructed on how to perform the following:

- How to take their study drug.
- [redacted]
- How to enter their study drug administrations in their diary.
- How to document whether they ate a meal before taking study drug.
- [redacted]

Re-education on proper administration procedures will be given to subjects by the site staff throughout the treatment period.

5.5.1 Overdose Management and Treatment

In the case of a suspected overdose, the subject will be instructed to contact the investigator or study coordinator immediately. Standard symptomatic support measures should be used in the case of excessive pharmacologic effects or overdose. No antidotes are currently available.

5.5.2 Missed Doses

If a dose is missed, subjects will be advised as follows:

- If within 4 hours from missed dose, dose immediately.
- If greater than 4 hours from missed dose, consider dose "missed" and resume regular dosing at next planned administration per protocol.

5.6 Masking

The clinical study will be performed in a double-masked manner. [redacted] The IWRS will assign study drug by kit number to each subject at the time of randomization. Only personnel in IWRS, clinical supplies, and plasma concentration analysis laboratory will be unmasked and will have access to treatment assignments; all other parties involved in the study will be fully masked.

5.6.1 Breaking the Mask

A subject's treatment assignment will not be broken until the EOS, unless medical treatment of the subject depends on knowing the study treatment the subject received. In the rare event that the mask needs to be broken because of a medical emergency, the investigator may unmask an individual subject through the IWRS. Reasons for treatment unmasking must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

Subjects who are unmasked will be allowed to continue their participation in the study; however, their data may be excluded from the per-protocol analyses. Unmasked subject data will be available to designated Senju personnel only; the mask will be maintained for all other Senju and PPD operational team members, as well as investigators and subjects.

5.7 Treatment Compliance

Subject compliance will be determined from subject study drug administration diaries and via examination of used study drug kits.

Subjects will be asked to complete an entry in the diary every time they take their study drug [redacted] The diary will be reviewed by the site staff at each

weekly study visit during the 12-week treatment period, and the subject will be re-educated on dose administration and/or diary entry as needed. The diary will also be reviewed at Week 16/EOS. The calculation for determining percentage compliance is presented in Section 7.8.

[redacted]

5.8 Prior and Concomitant Therapy

5.8.1 Recording of Prior and Concomitant Medications and Procedures

Any medicinal product prescribed or over-the-counter (OTC; including herbal and other nontraditional remedies), is considered a concomitant medication. At Screening, all prior medications used within 30 days will be recorded in the eCRF. At Day 1, prior medication use will be updated. The use of concomitant medications and procedures will be recorded in the eCRF beginning on Day 1 after the first dose of study drug until the EOS visit.

Prior and concomitant medications will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications will also be recorded in the subject's eCRF.

In subjects with bilateral wet AMD, the date of the last dose of anti-VEGF treatment in the fellow eye will be recorded.

5.8.2 Prohibited Concomitant Medications, Treatments, and Procedures

[Note: "Systemic" drug/medication use is defined as any medication that may ultimately affect the eye (specifically the retina) and is delivered by injection or oral methods.]

Prohibited medications, treatments, and procedures during the study (Screening through EOS) are as follows:

1. Anti-vascular endothelial growth factor agents (systemic use or administered via intravitreal injection to the study eye).

   Note: Injection of anti-VEGF into the fellow eye during the study period is prohibited. If the subject requires anti-VEGF treatment in the fellow eye, the subject should be discontinued from the study, and the EOT assessments should be completed.

[redacted]

[redacted]

5. Corticosteroids (systemic use or topical to the study eye, although topical dermal corticosteroid administration outside the periocular area is permitted per Exclusion Criteria 16 and 19).
    a. Intravitreal injection of an ocular corticosteroid in the study eye within 12 months prior to Day 1 is exclusionary.
    b. Sub-Tenon or subconjunctival injection of an ocular corticosteroid within 90 days of Day 1 is exclusionary. Systemic corticosteroid use by the subject within 28 days prior to Day 1 is exclusionary.
    c. Topical dermal corticosteroid use by study subjects that has been administered outside of the periocular region is permitted prior to and during subject study participation.
6. Photodynamic therapy (such as Vsudyne®), laser photocoagulation, radiation therapy, vitrectomy, or any other AMD treatment for the study eye.
7. Cataract surgery, other ocular surgeries, and use of contact lenses (including therapeutic lenses) for the study eye.

The use of concomitant medication may be warranted for the treatment of AEs. The use of concomitant medications to treat an AE will be at the discretion of the investigator.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an ICF. Potential subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the potential subject. The investigator (or designee) will also sign the ICF.

The EOT visit is defined as the visit occurring at the end of the 12-week treatment period (Week 12) or the final visit at which the subject is permanently discontinued/withdrawn from study drug administration. The EOS visit is defined as the visit occurring at the end of the 16-week study period (Week 16) or the final visit at which the subject is permanently discontinued/withdrawn from participation in the study.

The SOE is presented in Section 13 (Table 13–1). On Day 1 (SOT) and the EOT visit, all scheduled assessments must be completed in a single day. For all other visits, in the event that all of the scheduled assessments cannot be completed in a single day, the site staff must ensure that BCVA-ETDRS and OCT scan are performed on the same day.

6.1 Efficacy Assessments

Refer to the *MT-0814 Ophthalmology Procedure Manual* for detailed instructions on each of the ophthalmological assessments to be performed in this study. All imaging efficacy assessments will be measured/interpreted by a central reading facility.

6.1.1 Visual Acuity via Early Treatment of Diabetic Retinopathy Study

The BCVA of each subject will be assessed via the ETDRS without pupil dilation as indicated in the SOE (Table 13–1). The BCVA will be assessed for both the study and fellow eye of each subject at Screening, Day 1, the EOT visit, and the EOS visit. At all other visits, BCVA will be assessed for the study eye only. Refer to the *MT-0814 Ophthalmology Procedure Manual* for detailed instructions on BCVA-ETDRS assessment.

6.1.2 Optical Coherence Tomography

Optical coherence tomography will be performed with pupil dilation at every study visit as indicated in the SOE (Table 13–1). Optical coherence tomography will be performed on both the study and fellow eye of each subject at Screening, Day 1, the EOT visit, and the EOS visit. At all other visits, OCT scan will be performed on the study eye only.

Central subfield thickness will be measured at every visit via OCT scan. Assessment of dry retina (defined as an absence of visible intraretinal cystoid edema or subretinal fluid on OCT scan) will be performed on Day 1, Week 4, Week 8, the EOT visit, and the EOS visit. Refer to the *MT-0814 Ophthalmology Procedure Manual* for detailed instructions on the OCT procedure, as well as the assessments of CSFT and dry retina.

6.1.3 Fluorescein Angiography/Indocyanine Green Angiography

All study sites will perform FA, while select sites will also perform ICGA in addition to FA. Both FA and ICGA will be performed with pupil dilation on the subject's study eye only at Screening and the EOT visit (Table 13–1).

A single central reading facility will determine the CNV subtype (predominantly classic, minimally classic, occult with no classic type) and assess whether PCV and/or retinal angiomatous proliferation (RAP) is present in the study eye at Screening. The central reading facility will measure CNV area, total lesion area, leakage area, and polyp area (if PCV detected) in the study eye at the EOT visit. Refer to the *MT-0814 Ophthalmology Procedure Manual* for detailed instructions on the FA and ICGA procedures, as well as the assessment of CNV.

6.1.4 Color Fundus Photography

The CFP will be performed with pupil dilation as indicated in the SOE (Table 13–1). The CFP will be performed on both the study and fellow eye of each subject at Screening, the EOT visit, and the EOS visit. At all other visits, the CFP will be performed on the study eye only. The CFP images will include the periretinal area, macula, choroid, and vitreous humor. The following assessments are also regarded as safety assessments.

The following items will be assessed by the investigator at Screening and after Screening:

- Screening:
  - Absence/presence of retinal/subretinal hemorrhage
  - Absence/presence of serous retinal detachment
  - Absence/presence of rhegmatogenous retinal detachment
  - Absence/presence of vitreous hemorrhage
  - Absence/presence of vitreous opacity

- After Screening
  - Existence of worsening retinal/subretinal hemorrhage from Screening
  - Existence of worsening serous retinal detachment
  - Existence of worsening rhegmatogenous retinal detachment
  - Existence of worsening vitreous hemorrhage
  - Existence of worsening of vitreous opacity

6.2 Safety Assessments

6.2.1 Ophthalmological Assessments

Ophthalmological assessments will be performed at the indicated visits in the SOE (Table 13–1). Refer to the *MT-0814 Ophthalmology Procedure Manual* for detailed instructions on each of the ophthalmological assessments to be performed in this study. The examiners must use the same mode of measurement throughout the entire study and the assessments must be performed by the same evaluator.

Slit-lamp biomicroscopy will be performed on both the study eye and fellow eye of each subject at Screening, Day 1, the EOT visit, and the EOS visit. At all other visits, slit-lamp examinations (without pupil dilation) will be performed on the study eye only. Both slit-lamp procedures (biomicroscopy and examination) will evaluate the condition of the eyelids, conjunctiva, anterior chamber, cornea, and lens. Pupil dilation is not required for examination of the lens; lens examination will include an assessment of opacity via the Lens Opacities Classification System III (LOCS III).[16]

Measurement of IOP will be performed on both the study eye and fellow eye of each subject at Screening, Day 1, the EOT visit, and the EOS visit. At all other visits, IOP measurements will be performed for the study eye only. Intraocular pressure will be measured by the Goldmann tonometry method, with IOP recorded as millimeters of mercury (mm Hg).

6.2.2 Adverse Events

6.2.2.1 Definitions of Adverse Events

The investigator is responsible for reporting all TEAEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.2.2.2 Eliciting and Documenting Adverse Events

Adverse events will be collected and assessed from the time the subject signs the ICF until they exit from the study or 30 days after the last dose of the study drug, whichever is later. Any AE that occurs after the first dose of study drug is considered treatment-emergent.

Serious AEs that occur more than 30 days after exit from the study or 30 days after the last dose of study drug, whichever is later, will be reported to PPD/sponsor, only if the investigator considers them related to study drug.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory test results or physical examination findings) or identified from review of other documents (eg, subject diaries) that are relevant to subject safety.

6.2.2.3 Reporting Adverse Events

All AEs reported or observed after the subject signs the ICF will be recorded on the AE page of the eCRF. Information to be collected includes the following:

- Event term
- Time of onset
- Location of event (ocular or non-ocular); if location is an eye, the study or fellow eye must be identified)
- Investigator-specified assessment of severity
- Investigator-specified assessment of relationship to study drug, study procedure (procedure must be identified), or laboratory test result (laboratory test parameter must be identified)
- Date of resolution
- Seriousness
- Any required treatment or evaluations
- Any required changes in study drug administration (treatment interruption, dose change, treatment discontinuation, study withdrawal, or none)
- Outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the medical condition deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets the SAE criteria (Section 6.2.2.1) must be reported to the PPD Pharmacovigilance Department immediately (ie, within 24 hours) after the time the site staff first learn about the event. The following contact information is to be used for SAE reporting:

PPD Pharmacovigilance Department

SAE Hotline: [redacted]

SAE Fax line: [redacted]

6.2.2.4 Assessment of Severity

The intensity of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	These events require minimal or no treatment and do not interfere with the subject's daily activities
Moderate:	An AE that is sufficiently discomforting to interfere with normal activities
Severe:	These events interrupt a subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating

When changes in the severity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in intensity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended intensity grade and the date (and time, if known) of the change. Changes in the intensity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

6.2.2.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or

chemicals cannot explain. The response to withdrawal of the treatment (dechallenge*) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge† procedure, if necessary.

*Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed-drug eruptions, or tardive dyskinesia).

†Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is re-administered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

6.2.2.6 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

6.2.3 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the visits indicated in the SOE (Table 13–1). After Screening, all visits that include laboratory tests must occur after an 8-hour fast. Sample collection (blood, urine) should be performed before FA and ICGA are performed. Sample collection, processing, and shipping should be performed according to the local laboratory requirements.

Routine laboratory tests will be evaluated by a central laboratory and will include the following:

- **Hematology**: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and absolute platelet count.

- **Serum chemistry**: total protein, sodium, potassium, calcium, chloride, inorganic phosphate, albumin, fasting blood glucose*, glycated hemoglobin, total cholesterol, high-density lipoprotein and low-density lipoprotein† cholesterol, follicle-stimulating hormone, human chorionic gonadotropin (β-subunit), triglycerides, blood urea nitrogen, creatinine, uric acid, bilirubin (total and direct), alkaline phosphatase, aspartate aminotransferase, C-reactive protein, alanine aminotransferase, γ-glutamyltransferase, lactate dehydrogenase, and creatine kinase.

- **Urinalysis**: pH, glucose, ketones, specific gravity, nitrite, protein, bilirubin, urobilinogen, and blood. Microscopic urinalysis will be performed if urinalysis results are abnormal.

*Fasting at Screening is not required; therefore, glucose testing at Screening may be fasting or nonfasting. All subsequent laboratory tests should be performed after an 8-hour fast (see SOE, Table 13–1).

†Low-density lipoprotein will be directly measured (eg, beta-quantification [ultracentrifugation]) if a subject's triglyceride level is ≥400 mg/dL.

Serum pregnancy test: Serum pregnancy testing will be performed for all females at Screening (Visit 1) and the EOS visit.

Urine dipstick pregnancy test: On Day 1, a urine pregnancy dipstick test will be performed for all females who are either premenopausal or have been postmenopausal for <1 year to confirm their eligibility for assignment to study treatment.

Urine drug test: A screen for drugs of abuse will be performed at Screening and Day 1 according to the local laboratory standard practices.

6.2.4 Vital Sign Measurements

Vital sign measurements will be performed at the indicated visits in the SOE (Table 13–1). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mm Hg])
- Pulse (beats per minute)
- Body temperature (°C) (The method used to obtain a subject's body temperature at Screening should be used for that subject at all subsequent measurements)

- Height (cm) and body weight (kg). Height is to be measured at Screening only

Supine blood pressure, pulse, and body temperature (°C) will be recorded after the study subject has been recumbent and at rest for at least 5 minutes.

6.2.5 Physical Examination, Medical History, and Medication History

A limited physical examination will be performed at the indicated visits in the SOE (Table 13–1). The limited physical examination includes a review of the subject's medical history, medication history, and evaluation of relevant body systems complaints. In case of relevant findings, full evaluation of the condition needs to be conducted.

6.2.6 Electrocardiogram

A standard 12-lead ECG will be performed at Screening to assess eligibility to participate in the study; a subsequent 12-lead ECG will be performed at the EOT visit (Table 13–1). All ECGs will be reviewed by the investigator, and any findings will be documented on the ECG eCRF page.

6.2.7 Demographics

Demographics information will be collected at Screening as follows: age, race, iris color, and sex.

6.2.8 Eligibility

Eligibility will be evaluated at Screening and on Day 1 using the criteria outlined in Section 4.1. Subjects must meet all inclusion and none of the exclusion criteria to be considered eligible for the study.

6.2.9 Clinical Significance of Safety Assessments

Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (eg, vital sign measurements, ophthalmological assessments) — including those that worsen from Baseline — that are deemed to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

6.3 Pregnancy

Female subjects of childbearing potential (defined in Inclusion Criterion 10 of Section 4.1.1) and male subjects are required to use effective contraception throughout the study.

Acceptable methods of contraception for female subjects include oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted/injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides). Note: Female subjects who are actively practicing abstinence or who have a partner that is sterile (eg, vasectomy) will be permitted to participate in the study without contraception use.

The acceptable method of contraception for male subjects is the use of a condom plus spermicide. Note: Male subjects who are actively practicing abstinence or who have a partner that is sterile (eg, postmenopausal or undergone successful sterilization [both defined in Inclusion Criterion 10 of Section 4.1.1]) will be permitted to participate in the study without contraception use.

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to PPD/sponsor within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine its outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the health status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages and congenital abnormalities of the child must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after study completion, and considered by the investigator as possibly related to the study treatment, must be promptly reported to PPD/sponsor.

6.4 Assessment of Plasma Concentrations of MT-0814 and Metabolites

Plasma concentrations of MT-0814 and its metabolites M5 and M6 will be assessed on Days 1, 29, 57, and 85 (EOT). The plasma concentration sample collection schedule is presented in Table 13–2; on each of the days specified above and in the table, a single predose and a single 2-hour postdose blood sample will be collected for these assessments.

Subjects will be instructed to refrain from taking their study drug on the mornings of these scheduled blood collection days, and instead will be instructed to bring those doses to the site so that they can be taken after predose blood samples are collected.

Plasma concentrations of MT-0814 and the metabolites M5 and M6 will be determined by [redacted] (Table 11–1). Comprehensive PK analyses of MT-0814 and its metabolites will be performed in future studies.

Plasma samples remaining from PK analysis may be retained by the sponsor for additional investigations (ie, long-term stability and/or reproducibility).

6.5 Review of Concomitant Medications

Concomitant medication usage will be assessed at every visit starting at Day 1. Details for the recording of concomitant medications are in Section 5.8.1.

6.6 Dispensing of Study Drug

Study drug will be dispensed at the study visits indicated in the SOE (Table 13–1). Details on the management of clinical supplies, including accessing IWRS and dispensing masked study drug, for the study are in Section 5.4.

6.7 Review of Subject Diary for Compliance

Subject diaries will be reviewed for compliance by site staff at each study visit indicated in the SOE (Table 13–1). If compliance is suboptimal, the subject will be re-educated on the need to administer [redacted]

7 Statistical and Analytical Plan

A study eye will be identified for each subject; refer to Section 4.1 for the definition of the study eye. The nonstudy eye will be referred to as the fellow eye.

Unless otherwise specified, efficacy will be summarized for the study eye only. Ocular safety summaries by eye will be presented for the study eye, the fellow eye, and the worse eye where the worse eye is the eye that has the most negative response between the study and fellow eye for a given assessment/visit.

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline (Day 1) in BCVA at Week 12.

7.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the change from Baseline (Day 1) in CSFT at Week 12.

7.3 Other Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed:

- Changes from Baseline (Day 1) in BCVA by visit.
- Changes from Baseline (Day 1) in CSFT by visit.
- Proportions of subjects who achieve dry retina (defined in Sections 3.1 and 6.1.2) at Weeks 4, 8, 12, and 16.
- Changes from Baseline (Screening) in total lesion area (assessed via FA, ICGA, and CFP) at Week 12.
- Changes from Baseline (Screening) in CNV area (assessed via FA, ICGA, and CFP) at Week 12.
- Changes from Baseline (Screening) in leakage area (assessed via FA, ICGA, and CFP) at Week 12.
- Changes from Baseline (Screening) in polyp area (assessed via FA, ICGA, and CFP) at Week 12.
- Proportions of subjects who require rescue therapy (Section 4.2.3).

- Duration of time from Baseline (Day 1) to initiation of rescue therapy (Section 4.2.3).
- Proportions of subjects whose BCVA scores have increased/decreased by 5, 10, or 15 letters from Baseline (Day 1) to Week 12.

7.4 Sample Size Calculations

The sample size for this study was not selected based on statistical power calculations, but rather on clinical considerations. Approximately 35 subjects will be randomly assigned (in a 3:3:1 ratio) to receive MT-0814 [redacted] MT-0814 [redacted] or placebo [redacted] Randomization will be stratified by the BCVA score category (scores ≤55, 56 to 70, or ≥71) observed for the subject's study eye on Day 1 (Baseline).

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses:

- Full-analysis set (FAS): The FAS will consist of all participants who were randomly assigned to receive double-masked study drug and who have received at least 1 dose of study drug. All analyses using the FAS will group participants according to randomly assigned treatment.
- Per-protocol set (PPS): The PPS will consist of all FAS participants who meet all of the inclusion criteria and none of the exclusion criteria, have at least 75% compliance with study treatment, have not taken any of the prohibited medications listed in Section 5.8.2, and have no significant protocol deviations. Subjects will not be excluded from the PPS if they discontinued treatment due to lack of efficacy or if they have protocol deviations, including unmasking, that are attributable to lack of efficacy. All analyses using the PPS will group participants according to treatment actually received.
- Safety set (SS): The SS will consist of all participants who received any study drug. All analyses using the SS will group participants according to the treatment that is actually received.
- MT-0814 plasma concentration data set: The PK data set will consist of plasma concentration data of samples obtained from all participants who received any active study drug.

The FAS and PPS will be used for the efficacy analysis with the primary population for analysis being the FAS. Safety will be summarized using the SS.

7.6 Description of Subgroups to be Analyzed

Efficacy summaries will also be presented for the following subgroups:

- CNV type (predominantly classic, minimally classic, occult with no classic type; refer to Section 6.1.3)
- Presence/absence of PCV (only if a sufficient number of subjects with PCV are assessed)
- Presence/absence of RAP (only if a sufficient number of subjects with RAP are assessed)
- BCVA at Baseline (Day 1)
- Age
- Sex
- Body mass index

7.7 Subject Demographics and Other Baseline Characteristics

Descriptive statistics will be provided by treatment group for subject demographics and all ocular and Baseline characteristics. Relevant medical history (ocular and nonocular) and current medical conditions will be tabulated by treatment group. Ocular summaries will be presented for the study eye and the fellow eye. Other relevant Baseline information will be listed and summarized as appropriate with descriptive statistics. Analyses will be based on the FAS, PPS, and SS.

7.8 Treatment Exposure and Compliance

As noted in Section 5.7, subjects will be asked to complete a daily diary noting each administration of study drugs and compliance will be calculated based on the diary data. Descriptive statistics will be provided to characterize study treatment exposure and compliance using the FAS, PPS, and SS. Duration of exposure will be calculated in days as the (date of last dose – date of first dose + 1). [redacted]

7.9 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or higher. Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan (SAP).

All statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% (2-sided) confidence intervals. Pairwise comparisons will be performed with no multiplicity adjustments. Additionally, no multiplicity adjustments will be performed for multiple endpoints.

7.9.1 Analysis of Primary Efficacy Endpoint

The primary analysis will be performed on the study eye within the FAS. The following 2-sided hypothesis will be tested:

- Ho: The difference in mean change from Baseline in BCVA in the study eye at Week 12 between placebo and MT-0814 is equal.
- Hø: The difference in mean change from Baseline in BCVA in the study eye at Week 12 between placebo and MT-0814 is not equal.

The primary analysis will be performed using an analysis of covariance (ANCOVA) model including fixed effect for treatment and Baseline BCVA score as a covariate. Subjects with missing data at Week 12 or who receive rescue therapy will have their data imputed by worst observation carried forward (WOCF) method. Only postbaseline observations observed prior to dropout or receipt of rescue therapy (whichever occurs first) will be carried forward. Additional sensitivity analyses such as the following may be performed:

- An ANCOVA on observed data
- A t-test on observed data
- The mixed models repeated measures (MMRM) including observed data for all visits through Week 12

- The ANCOVA at Week 12 incorporating data from the fellow eye with missing data at Week 12 imputed using WOCF. (This analysis will be dependent on the number of subjects who have both eyes meet all entry criteria.)

- Multiple imputations of missing data analyzed using the same ANCOVA model as for the primary analysis.

Analysis will be performed separately to compare each dose of MT-0814 to placebo (eg, including only subjects receiving placebo and subjects receiving the MT-0814 dose being compared to placebo.)

The change from Baseline in BCVA at Week 12 will be also be descriptively summarized by the subgroups presented in Section 7.6. Statistical hypothesis testing to compare each MT-0814 dose to placebo within subgroups will be performed by t-test if the subgroup size is sufficient.

7.9.2 Analysis of Key Secondary Efficacy Endpoint

The primary analysis of change from Baseline in CSFT at Week 12 will be performed using an ANCOVA model including fixed effect for treatment and Baseline CSFT score as a covariate. Missing data or data after receipt of rescue medication will be imputed using WOCF. Selected sensitivity analyses like those identified for the primary efficacy endpoint may also be performed. Analysis will be performed separately to compare each dose of MT-0814 to placebo (eg, including only subjects receiving placebo and subjects receiving the MT-0814 dose being compared to placebo).

7.9.3 Analyses of Other Secondary Efficacy Endpoints

Endpoints for changes from Baseline at each visit will be analyzed using an ANCOVA model, applying treatment as fixed effect and the parameter's Baseline value as the covariate, utilizing WOCF for missing data or treatment data occurring after receipt of rescue therapy. The t-tests will also be performed for changes from Baseline. Endpoints for proportions of subjects will be analyzed using Fisher's Exact test. Kaplan-Meier estimates will be presented for the time to receipt of rescue therapy.

Analyses will be performed separately to compare each dose of MT-0814 to placebo (eg, including only subjects receiving placebo and subjects receiving the MT-0814 dose being compared to placebo).

7.9.4 Safety Analyses

Safety parameters include monitoring of AEs, TEAEs, physical examination findings, vital sign measurements, laboratory tests, ECG results, visual acuity, slit-lamp biomicroscopy, and IOP.

Safety data will be summarized and listed with no statistical hypothesis testing performed. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

7.9.4.1 Adverse Events

All AEs will be listed and all TEAEs will be summarized. Adverse events will be deemed treatment-emergent if the onset date is on or after the date of first treatment, Day 1. Events that are not treatment emergent will be listed separately and together with all other AEs. Ocular TEAEs will be summarized separately from non-ocular TEAEs. Ocular TEAEs will be summarized for the study eye, the fellow eye, and either/worse eye (eg, a subject will be counted if the given event occurred in either the study or fellow eye. When events are summarized by relationship or severity, the event with the greatest relationship or severity will be used).

Treatment-emergent AEs will be summarized by treatment group, presenting the number and percentage of subjects having a TEAE in each system organ class and having each individual TEAE based on the preferred term. Additionally, TEAEs will be summarized by the number of events per 100 person-years of follow-up. Treatment-emergent AEs will also be tabulated according to intensity and causality. Subjects who experienced multiple TEAEs for a preferred term (PT) will be counted once, similarly for subjects with multiple TEAEs per system organ class (SOC).

Deaths, SAEs, and TEAEs leading to discontinuation of study drug will be listed separately and, if appropriate, summarized by treatment group, SOC, and PT.

The incidence of AEs over time may also be summarized.

7.9.4.2 Physical Examinations

Abnormal physical examination findings will be listed.

7.9.4.3 Vital Sign Measurements

Observed values for vital sign measurements at Baseline and Weeks 4, 8, 12 (EOT), and 16 (EOS) — as well as changes from Baseline to postbaseline values in vital sign measurements — will be summarized descriptively by treatment group. All vital sign measurement data will be listed.

7.9.4.4 Clinical Laboratory Tests

Observed values for clinical laboratory tests (hematology, serum chemistry, and urinalysis) at Screening, Weeks 4 and 8 (serum chemistry only), Week 12 (EOT), and Week 16 (EOS) will be summarized descriptively by treatment group. Additionally, shift tables will be presented for all clinical laboratory test parameters from Screening to Week 12 (EOT) and Week 16 (EOS), and for serum chemistry test parameters from Screening to Week 4 and Week 8. All clinical laboratory test data will be listed.

7.9.4.5 Electrocardiograms

Electrocardiogram findings will be evaluated by the following criteria:

- Normal
- Abnormal (not clinically significant)
- Abnormal with clinical significance (clinically significant).

7.9.4.6 Slit-Lamp Biomicroscopy

Ocular findings (excluding lens opacity assessments that are obtained via LOCS III[16]) will be evaluated by the following criteria:

- Normal
- Abnormal (not clinically significant)
- Abnormal with clinical significance (clinically significant)

Data from all slit-lamp biomicroscopy assessments will be listed. Shift tables will present the number and percentage of subjects in each cross-categorization results from Baseline to the worst postbaseline assessment by parameter and will be summarized for the study eye, fellow eye, and worse eye. Percentages will be calculated using the number of subjects in the SS who have data at Baseline and at least 1 postbaseline assessment.

Lens opacity will be assessed using LOCS III criteria[16] to assess nuclear color/nuclear opalescence, cortical cataract, and posterior subcapsular cataract. Lens opacity findings will be summarized in a similar manner in that shift tables will present the number and percentage of subjects in each cross-categorization results from Baseline to the worst postbaseline assessment by parameter and will be summarized for the study eye, fellow eye, and worse eye. Percentages will be calculated using the number of subjects in the safety set who have data at Baseline and at least 1 postbaseline assessment.

7.9.4.7 Intraocular Pressure

All IOP data will be listed. Observed IOP values at Baseline and each subsequent study visit, as well as changes from Baseline in IOP for each subsequent study visit, will be summarized descriptively by treatment group for the study eye, fellow eye, and worse eye (eg, highest IOP value).

7.9.5 Interim Analyses

No interim analysis will be performed for this study.

8 Data Quality Assurance

The sites will maintain source documentation and enter subject data into the eCRF as accurately as possible and will rapidly respond to any reported discrepancies. The eCRFs are accessed through Medidata Rave (Medidata Solutions Inc, New York, New York). This electronic data capture system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11. Each person involved with the study will have an individual user name and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. A quality review of the data will be performed by the site with additional reviews by the clinical monitor through source data verification.

Each eCRF is presented as an electronic copy, allowing data entry by site staff, who can add and edit data, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed by the investigator. This system provides site staff, monitors, and reviewers with access to hard copy audits, discrepancy reviews, and investigator comment information.

After all data reviews and query resolutions are complete, the SAP is approved and signed, and any summary/analysis populations are approved, the database will be locked.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diary cards, laboratory test reports, etc. All eCRF information is to be completed. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

Investigative site personnel will enter subject data into an electronic data capture system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory test data).

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and medical history will be coded using MedDRA terminology. Concomitant medications will be coded using the World Health Organization Drug Dictionary.

After database lock, each study site will receive an electronic copy of their site-specific eCRF data as entered into the electronic data capture system for the study, including full discrepancy and audit history. Additionally, an electronic copy of all of the study site's data from the study will be created and sent to the sponsor for storage. PPD will maintain a duplicate electronic copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB) before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6: Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB.
The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3 Subject Information and Consent

A written ICF in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An ICF template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject or legal guardian.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

10.1 Confidentiality

All laboratory test specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA), or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- Approval of the IRB,
- Original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572,
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,
- Informed consent form approved by the IRB, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The administrative structure is presented in Table 11–1.

Table 11–1 Study Administration

Role	Name/Affiliation/Address
Sponsor	Senju Pharmaceutical Co., Ltd. 3-1-9, Kawaramachi, Chuo-Ku, Osaka 541-0048, Japan
Sponsor Signatory	[redacted]
Sponsor Pharmacovigilance	[redacted]
Contract Research Organization	[redacted]
Study Medical Monitor	[redacted]
Study Drug Manufacturing Facilities	[redacted]
Central Laboratory	[redacted]
Plasma Concentration Analysis Laboratory	[redacted]

11.1 Monitoring

11.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study

subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Senju Pharmaceutical Co., Ltd. has every intention of completing the study, Senju Pharmaceutical Co., Ltd. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last subject completes the last visit (ie, Week 16).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary

results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

[redacted]

5. Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PT, et al; Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004;122(4):564-72.

6. Kocur I, Resnikoff S. Visual impairment and blindness in Europe and their prevention. Br J Ophthalmol. 2002;86(7):716-22.

7. Miyazaki M, Nakamura H, Kubo M, Kiyohara Y, Oshima Y, Ishibashi T, et al. Risk factors for age related maculopathy in a Japanese population: the Hisayama study. Br J Ophthalmol. 2003;87(4):469-72.

8. Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, et al. Prevalence of age-related macular degeneration in Europe: the past and the future. Ophthalmology. 2017;124(12):1753-63.

9. Lopez PF, Sippy BD, Lambert HM, Thach AB, Hinton DR. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. Invest Ophthalmol Vis Sci. 1996;37(5):855-68.

10. Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. Invest Ophthalmol Vis Sci. 1996;37(9):1929-34.

11. EYLEA (aflibercept injection) United States prescribing information. Regeneron Pharmaceuticals, Inc.; Tarrytown, NY, USA; May-2017.

12. LUCENTIS (ranibizumab injection) United States prescribing information. Genentech; San Francisco, CA, USA; March-2018.

13. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432-44.

14. Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. Am J Ophthalmol. 2008;145(2):239-48.

15. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014;121(1):193-201.

16. Chylack LT Jr, Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol. 1993;111(6):831-6.

13 Schedules of Study Events

Table 13–1 Schedule of Study Drug Administration, Examinations, and Observations

Visit No.	1	2[a] (RAN/ SOT)	3	4	5	6	7	8	9	10	11	12	13	14[b] (EOT)	15	16	17	18[c] (EOS)
Study Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Day: (Allowance):	**≤14 Days Before Day 1**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**43 (±2)**	**50 (±2)**	**57 (±2)**	**64 (±2)**	**71 (±2)**	**78 (±2)**	**85 (±2)**	**92 (±2)**	**99 (±2)**	**106 (±2)**	**113 (±2)**
Informed Consent	X																	
Demographics	X																	
Eligibility (Inclusion/Exclusion Criteria)	X	X																
Study Drug Administration		X →	→	→	→	→	→	→	→	→	→	→	→	X[j]				
ETDRS BCVA[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optical Coherence Tomography[d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Biomicroscopy[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography[d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FA/ICGA Screening[f]	X													X				
Vital Signs[g]	X	X				X				X				X				X
Physical Exam, Medical/Medication History	X	X												X				X

Visit No.	1	2[a] (RAN/ SOT)	3	4	5	6	7	8	9	10	11	12	13	14[b] (EOT)	15	16	17	18[c] (EOS)
Study Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Day: (Allowance):	**≤14 Days Before Day 1**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**43 (±2)**	**50 (±2)**	**57 (±2)**	**64 (±2)**	**71 (±2)**	**78 (±2)**	**85 (±2)**	**92 (±2)**	**99 (±2)**	**106 (±2)**	**113 (±2)**
Electrocardiogram	X													X				
Hematology	X													X				X
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Urinalysis	X													X				X
Plasma Concentration Analysis Sampling[h]		X				X				X				X				
Serum Pregnancy Test[i]	X																	X
Urine Dipstick Pregnancy Test[i]		X																
Urine Drug Test	X	X																
Study drug dispensed		X				X				X								
Concomitant medications reviewed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject diary reviewed			X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BCVA = best-corrected visual acuity; [redacted] EOS = end of study; EOT = end of treatment; ETDRS = Early Treatment of Diabetic Retinopathy Study; FA = fluorescein angiography; ICGA = indocyanine green angiography; OCT = optical coherence tomography; [redacted] RAN = randomization; SOT = start of treatment.

a) At this visit, subjects who meet all eligibility criteria for the study will be randomly assigned in a 3:3:1 ratio to receive MT-0814 [redacted] MT-0814 [redacted] or placebo [redacted] All randomized subjects will be administered their first dose of study drug during this visit (preferably before 12 PM [Noon]).

b) The assessments included in this column must be conducted at the last subject visit for those who are discontinued or withdraw from the study before receiving 12 weeks of treatment.

c) The assessments included in this column must be conducted at the last subject visit for those who are discontinued or withdraw from the study before the end of the 4-week follow-up period.

d) Both the study eye **and** fellow eye will be assessed at Screening, Day 1 (no color fundus photography, FA, or ICGA assessments on Day 1), Visit 14 (Week 12; EOT), and the EOS/discontinuation visit (Visit 18 [Week 16] or early discontinuation/withdrawal). At all other indicated visits, only the study eye will be assessed.

e) Assessment of dry retina (defined as an absence of visible intraretinal cystoid edema or subretinal fluid on OCT scan) will be performed at Visit 2 (Day 1), Visit 6 (Week 4), Visit 10 (Week 8), Visit 14 (Week 12; EOT), and the EOS/discontinuation visit (Visit 18 [Week 16] or early discontinuation/withdrawal).

f) The FA will be performed at all sites; select sites will also perform ICGA in addition to FA.

g) Blood pressure, pulse, body temperature, and body weight will be assessed at all indicated visits; height will only be assessed at Visit 1.

Visit No.	1	2[a] (RAN/ SOT)	3	4	5	6	7	8	9	10	11	12	13	14[b] (EOT)	15	16	17	18[c] (EOS)
Study Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Day: (Allowance):	**≤14 Days Before Day 1**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**43 (±2)**	**50 (±2)**	**57 (±2)**	**64 (±2)**	**71 (±2)**	**78 (±2)**	**85 (±2)**	**92 (±2)**	**99 (±2)**	**106 (±2)**	**113 (±2)**

h) The detailed blood sample collection schedule for plasma concentration analyses is presented in Table 13–2.

i) Female subjects only. Day 1 urine dipstick pregnancy test will only be administered to female subjects who are either premenopausal or have been postmenopausal for <1 year.
Note: If a female subject has a positive pregnancy test result (serum and/or urine dipstick) but the investigator suspects that the result is a false positive, the female subject can participate in the study at the investigator's discretion.

[redacted]

Table 13–2 Schedule of Blood Sample Collection for Plasma Concentration Determination of MT-0814 and its Metabolites M5 and M6

		PK Blood Sample Collection Time	
		Predose	Postdose
Study Day	Dose Time	0	2 hours (±30 minutes)
1	AM	X	X
29	AM	X	X
57	AM	X	X
85	AM	X	X

Abbreviations: PK = pharmacokinetics.