**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY**

**AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION**

|  |  |
| --- | --- |
| **Sponsor / Study Title:** | **Kyowa Kirin Co., Ltd. / “A Phase 2, Multicenter, Randomized, Double-Masked, Parallel-Group Study to Assess the Efficacy and Safety of KHK4951, a Vascular Endothelial Growth Factor Receptor Inhibitor, in Patients with Diabetic Macular Edema”** |
| **Protocol Number:** | **4951-003** |
| **Principal Investigator:****(Study Doctor)** | **John Carlson, MD** |
| **Telephone:** | **909-335-8940 (24 Hour)** |
| **Address:** | **Retina Consultants of Southern Ca****1895 Orange Tree Lane****Suite 204****Redlands, CA 92374** |

# WHY HAVE I BEEN GIVEN THIS FORM?

You are being asked to participate in this **study** because you have diabetic macular edema (DME) and may satisfy the entry criteria for this study.

This form includes general information about a study called 4951‑003. It explains the procedures and treatments involved. Knowing what is involved will help you decide if you want to take part in the study.

If you have difficulty reading this form by yourself, an impartial witness can read the form instead.

Kyowa Kirin Co., Ltd. is the **Sponsor** for this study, a company based in Japan.

# DO I HAVE TO TAKE PART?

Your participation in this study is voluntary, which means that you can choose whether or not you want to participate. If you decide not to take part, there will be no loss of benefits to which you are otherwise entitled, and this will not affect the care you get from your doctors in any way.

You can stop taking part in the study at any time and without giving a reason. You are strongly advised to talk to your study doctor or study staff first. They can advise you about any concerns you may have and will answer your questions.

You may be asked to stop the study for reasons other than your own decision to stop, for example if the Sponsor decides to stop the study (which can be for safety reasons, or the drug being studied is not working as well as expected) or if the study doctor decides it is no longer benefitting you or due to your behavioral reasons. The research study can be stopped as well by regulatory health agencies, such as the US Food and Drugs Administration (FDA), and Institutional Review Board, which make sure research studies are run in an ethical way.

Before you make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do to participate. The ophthalmologist (eye doctor) who is working on this study (study doctor) and their study assistant (the study coordinator) will explain the study to you, and they have given you this consent form to read.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend, or your local doctor.

If you decide you want to take part in the study, you will be asked to sign the consent section, and you will be given a copy of this consent form to keep for your records. By signing it you are telling us that you:

* + Understand what you have read.
	+ Consent to take part in the study.
	+ Consent to have the procedures and treatments that are described.
	+ Consent to the use and storage of your personal and health information as described.

# WHAT IS THE STUDY ABOUT?

DME is swelling in the macula, or central part of the retina (inner lining of the eye that generates vision) of your eye, and the main cause of vision impairment in diabetic patients. DME happens when high blood sugar levels affect the blood vessels in your eyes, making them weaker and more likely to leak fluid and/or blood. It may also cause new and more fragile blood vessels to grow where they shouldn’t grow (new blood vessel growth). Leaking of fluid from blood vessels causes fluid build-up and thickens the retina which may result in loss of vision. Vascular endothelial growth factor (VEGF) is a protein that plays a significant role in new blood vessel growth called neovascularization. VEGF binds to its VEGF receptors which are present on the cell surface to enable the activation of the VEGF receptors, thereby exerting its new blood vessel growth activity.

The experimental drug being tested in this study is KHK4951 (eye drops). KHK4951 is expected to inhibit phosphorylation (activation) of VEGF receptors (called anti-VEGF treatment) and thus to prevent vascular hyperpermeability (a condition in which the walls of blood vessels in the retina become more permeable [easier for substances to pass through] than normal), which will help prevent the progression of diseases such as DME. KHK4951 has not yet been approved by the regulatory authorities in any country. However, an oral medicine called tivozanib sold under the brand nameFotivda that has the same active ingredient as KHK4951 has already been approved to be used for cancer in the European Union countries and the United States.

As of 04 Jul 2023, approximately 94 healthy volunteers and participants with neovascular age‑related macular degeneration (nAMD: also known as “wet” AMD), a retinal eye disease that is also characterized by new blood vessel growth, have received KHK4951 in one completed study. No death, no serious side effects, or no severe side effects have been reported. Details of safety information of KHK4951 can be found in the What are the Possible Risks Section. This study you are invited to take part in is the first KHK4951 study for patients with DME.

This study, called 4951-003, also uses aflibercept (eye injection) as the treatment before starting KHK4951 eye drop treatment as well as rescue treatment if deemed necessary by the study doctor. Aflibercept is another anti-VEGF treatment approved by local (national/regional) regulatory health agencies worldwide for the treatment of DME and other retinal eye diseases. Aflibercept interferes with the growth of new vessels and prevents leakage of fluid from new vessels.

The study involves research. The purpose of the study is to see if KHK4951, at different dose levels, is safe, tolerable (how well your body can accept KHK4951 without experiencing significant discomfort or side effects), and effective in treating your DME after the initial five monthly (every four weeks) aflibercept injections into your eye. In addition, this study will also help determine how KHK4951, at different dose levels, behaves inside the human body and how it is removed from the human body when given to DME patients treated with aflibercept.

Approximately 150 participants from four counties (United States, Japan, South Korea, and Australia) are expected to take part in this study.

In this study, you will initially receive aflibercept to check your response to aflibercept, and then you will be assigned to KHK4951 eye drop treatment if your response to aflibercept meets the response criteria. There are three possible study treatment arms with different dose levels of KHK4951 to which you may be allocated according to a **randomized** design. The probability for random assignment to each arm is 33% (1:1:1). As this is a **double‑masked** study, neither you nor the study doctor/Sponsor will know which arm you are in. However, the study doctor will be able to find out which arm you are in if it is necessary for safety reasons. You may also receive **placebo** to maintain the masking depending on the assigned treatment arm. In this document, KHK4951 or placebo is called investigational eye drops.

This study has an optional part that involves the collection, storage, and use of a blood sample from you for pharmacogenetic research, which is a study to investigate how your genes can influence the way your bodies respond to medications. You will receive a separate informed consent form for this optional part; please refer to that document for details.

Kyowa Kirin, the sponsor, its collaborators in the study or those developing the study drug, and their affiliates, representatives, agents and contractors including the contract research organization, Parexel, will measure the amount of study drug in your blood. This type of testing is called pharmacokinetics (PK) and measures the amount of the study drug in your blood and tells researchers how much time it takes for the study drug to be absorbed into your body and how long it stays in your body after it has been absorbed.

This research is important to doctors, like yours, because it can help your doctors understand why some people like you might benefit from some medicines while others do not. Sometimes this research can also help explain why some people are more likely to have a bad reaction to medicines.

Serum samples for pharmacokinetic tests will be stored at the bioanalytical facility until the final report is completed. Remaining serum samples after the competition of the final report will be discarded in a respectful manner as soon as they are no longer required.

# WHAT WILL HAPPEN TO ME DURING THE STUDY?

Before you begin the study, you will be given a complete explanation (verbally and with this document) of the nature and purpose of the study by the study doctor or their designee. If you decide to participate in the study, you will be asked to sign and date the consent statement at the end of this form. No study-related procedures will be done until you provide your consent.

This study consists of four periods listed below. In total, the study will last up to 60 weeks for you. You will be asked to visit the study site approximately 16 times during the study. Your study doctor may also ask you to attend extra visits if they feel it is necessary for your safety.

* **Screening period**: Up to 30 days prior to the first eye injection of aflibercept.
During this period, you will be assessed to determine if you are eligible to be in this study. If you have DME in both eyes, the eye with worse vision at screening will be selected as the study eye.

Some of the screening examinations may be repeated. Screening examinations may take place over multiple days. In such cases, you may need to visit the study site several times during this period.
Images from previous eye examinations (**fluorescein angiography**) may be used as part of your screening examinations as long as they were performed within 30 days of the date of first aflibercept injection.

* **Run-in period**: 16 weeks.
During this period, you will visit the study site five times. You will receive aflibercept injections in the study eye every four weeks during this period (up to five injections) to confirm response to aflibercept. If the study doctor confirms that you have responded to the first four injections of aflibercept at the 16th week visit to the study site, you will be randomly assigned (like drawing straws) to one of KHK4951 treatment arms and you will receive the fifth injection of aflibercept. In addition, you will be given investigational eye drops (KHK4951 and placebo, if applicable, according to the assigned study treatment arm) to take home.
If the study doctor considers you haven’t responded to aflibercept according to the study’s predefined criteria at the 16th week visit, you will be withdrawn from the study. You are still eligible to receive the fifth aflibercept injection into your eye per the approved standard of care schedule of aflibercept in DME without additional expense to you.
* **Study Treatment period**: 36 weeks; from one day after the 16th week visit to the study site and until the 52nd week visit to the study site.
You will see the study doctor every four weeks for 36 weeks starting from the 20th week visit to the study site (in total nine times).

During this period, you will receive the **study treatment** as described in the Study Treatment Section.

* **Follow-up period**: Up to four weeks after the end of study treatment or before you initiate new therapy after the last study treatment, whichever comes first.
During this period, you will be asked to complete follow-up assessments. The assessments will be performed at the study site or via phone call, depending on the study status and at the study doctor’s discretion.

During these visits, you will have the following procedures:

* **Blood tests**:
	+ To check your overall well-being.
	+ To check the levels of KHK4951 in your blood. Note that the remaining blood samples will be stored for future research.

The total amount of blood collected during the study will be approximately 154 mL (10 tablespoons), and approximately 22 mL (1.5 tablespoons) per sampling point.

* **Urine tests** to check your overall well-being.
* **Pregnancy test** if you are female who can get pregnant.
This test will be done using your urine. Additional pregnancy tests may be performed at any time during the study as required.
* **Eye examinations**: You will be examined by the study doctor who will check how your eyes are doing and you will have your vision tested.
	+ Intraocular pressure, slit-lamp examination of the anterior segment, fluorescein staining of the cornea, dilated fundus examination/indirect ophthalmoscopy, best-corrected visual acuity, spectral domain-optical coherence tomography (SD-OCT): These assessments will be performed on either the study eye only or both of your eyes depending on the visits. Please see Supplemental Information Sheet 2: Assessments for more details.
	+ Iris transillumination, color fundus photography, fluorescein angiography: These assessments will be performed on both of your eyes.
* **Specular microscopy**This assessment will be performed on both of your eyes.
This assessment will be performed at selected study sites only. Therefore, you may not undergo this assessment.
* **Interview** by the study doctor to assess the influence of visual disability and visual symptoms on generic health.
* **Electrocardiograms (ECGs)** (heart trace): You will be asked to take adequate rest in a supine position (lying on your back) before ECG measurement.
* Measurement of **vital signs** (body temperature, blood pressure, and pulse rate) and height and weight.
You will be asked to take an adequate rest before vital sign measurement in a supine, semi-supine (half-sitting) or sitting position.
* **Physical examinations** to monitor you for changes in symptoms and signs or new symptoms and signs.
* You will also be asked about **demographic information** (sex, ability to get pregnant [if you are female], age, race/ethnicity), medical history, smoking history, side effects, and concomitant medications and therapies. Please note that your participation will not be affected by your sex or race/ethnicity. You may be asked to provide your medical record of the hospitalization.

Refer to Supplementary Information Sheet 1: Glossary of Terms, Supplemental Information Sheet 2: Assessments and Supplementary Information.

## Study Treatment

During the run-in period, you will receive aflibercept injections in the study eye every four weeks for up to 16 weeks (up to five injections). Aflibercept is given by injection into the vitreous of the eye through the sclera after appropriate numbing and cleaning of the site of the injection (the sclera is the “white of the eye” and the vitreous is the clear, jelly‑like substance in the middle of the eyeball). The procedure is called an “intravitreal injection”. You will receive the fifth injection of aflibercept at the 16th week visit when the study doctor confirms that you responded to the first four injections of aflibercept. If you do not meet the study’s predefined criteria, the fifth injection of aflibercept will be optional.

During the study treatment period, you will receive investigational eye drops twice daily in the study eye, one drop each in the morning and in the evening from the day after the 16th week visit until one day prior to the 52nd week visit. Note that there are two separate bottles, one for morning and another for evening. The interval between each eye drop should be approximately 12 hours. Daily administration must be completed during the day (0:00 AM to 11:59 PM). Before administering eye drops, eye drop bottles should be shaken (approximately 20 times for 10 seconds).

If you are judged to be capable of adequate administration, you can administer investigational eye drops at home. If you have difficulty self‑administering, you can designate someone (such as a caregiver or family member) capable to administer investigational eye drops to your study eye. You will be provided an electronic diary (eDiary) to enter the following information about your investigational eye drops administration: date and time of administration, whether planned dose was administered or not, and details of inappropriate dose administration. On the days of visiting the study site, you will visit the study site after administering investigational eye drops in the morning at home.

At a visit to the study site during the study treatment period, you may receive aflibercept injections as rescue treatment (treatment given along with investigational eye drops) if deemed necessary by the study doctor.

## Drug Access after Study Completion

You will be given KHK4951 only during the study but not after it has ended.

# WHAT WILL I HAVE TO DO DURING THE STUDY?

Please inform the study doctor if you will not be able to attend a visit.

You should report any changes to your well-being, including any side effects, to the study doctor.

It is also important that you tell the study staff about any other medications you are taking before and during the study. Please tell the study doctor before you start a new medication. There may be some medications that are affected by the experimental drug used in this study. The study doctor will discuss with you any medications and therapies you should not take during the study.

You must not tell any information about the appearance of the investigational eye drops (e.g., bottle shape, color of contents) to any site staff except to the unmasked site staff.

You have to take eDiary home and record the daily investigational eye drops treatment using that eDiary device (iPad) at home.

You have to store investigational eye drops in a refrigerator (2°C to 8°C [36°F to 46°F]) at home in facing up position. If the investigational eye drops are left outside of the refrigerator, please contact the unmasked site staff.

You should keep all the bottles and cartons of investigational eye drops and you should bring them (including the ones with residual drug solution and empty ones) at each visit to the study site. You are requested to return unused investigational eye drops.

The effects of KHK4951 and aflibercept on an unborn child, infant, or pregnant women are not known. It is also not known whether KHK4951 has an effect on sperm or eggs (ova), whether it is found in semen or breast milk, or whether it has an effect on an unborn fetus or a baby. However, tivozanib is known to cause fetal harm when administered orally to a pregnant woman based on its mechanism of action and findings in animal studies. When pregnant animals were given tivozanib orally, it caused abnormal effects on the fetus and mother, birth abnormality, and death of the fetus. When male animals were given tivozanib orally, the male reproductive organs showed signs of being larger than usual, and the males had trouble reproducing and were unable to have offspring. In addition, it is not known whether aflibercept has an effect on sperm or eggs (ova), whether it is found in semen or breast milk, or whether it has an effect on an unborn fetus or a baby. However, administration of aflibercept in pregnant animals caused side effects on the fetus. Aflibercept should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Therefore, you (or your female partner) must not get pregnant or breastfeed a child during the period specified below.

* + If you are male, you have to practice true abstinence (practice of refraining from sexual activity) or use two adequate forms of highly effective birth control methods from the start of receiving the investigational eye drops until four weeks after the last investigational eye drops administration. Please check with the study doctor about what kind of birth control methods to use. In addition, you should not donate sperm during the study and for four weeks after the last investigational eye drops administration.
	+ If you are female, you have to practice two forms of highly effective birth control methods from the time of informed consent to three (3) months after the last aflibercept administration or one (1) month after the last investigational eye drops administration, whichever occurs later. Please check with the study doctor about what kind of birth control methods to use.
	+ If you or your partner becomes pregnant, you must tell the study doctor immediately. Your partner will be asked to sign a separate consent to provide information about her and her baby.

You should refrain from taking St John’s wort (including food and beverages containing St John’s wort) from 14 days before the date of first aflibercept injection to the end of study.

You should avoid excessive smoking, drinking alcohol, and the use of nicotine‑containing products from the time of providing written informed consent to the end of study.

You should stop wearing contact lens in the study eye from 7 days prior to the date of first aflibercept injection to the end of study, and meanwhile wear your spectacles as necessary.

You will receive eye drops to dilate or enlarge the pupil (the circular black area in the center of an eye) during the visits to the study site. The effect of this drug (vision blurred) may persist for some hours. Therefore, you will need to stay at the study site until these effects disappear. In addition, please do not visit the study site by driving a car, bike, or bicycle because it is still dangerous to drive these even after the effect of the drug ends.

When you see another doctor (e.g., your home doctor), please let the doctor and staff of that hospital know that you are participating in this clinical study.

If you notice anything about quality of the investigational eye drops (e.g., damaged bottle, cloudy, foreign matter, variation in product color), please contact the unmasked site staff at the phone number listed on page 1 of this form.

# WHAT ARE THE POSSIBLE RISKS?

As with all studies, KHK4951, aflibercept, and study procedures may involve unknown risks. Any medication can have temporary and permanent side effects and can cause unforeseen side effects, although not everyone gets them.

**Risks of KHK4951 reported in one completed study**

In the completed study, where participants received a single dose or multiple doses (average 21 days of study treatment) of KHK4951, KHK4951 was well tolerated. There were no deaths, no serious side effects, no severe side effects, or no side effects leading to discontinuation or interruption of KHK4951.

The most frequently reported side effect in the eyes in nAMD patients (after average 21 days of KHK4951 treatment) were:

* Punctate keratitis (damage to the cells of the cornea [clear part at the front of the eye]’s outer layer) (more than 25%)
* Eye irritation (20.0%)

**Risks of tivozanib**

The risks of KHK4951 are similar to that of tivozanib. However, as the route of administration of KHK4951 (eye drop) is different from that of tivozanib (oral) and a limited number of people had received KHK4951 at the time of initiating this study, the risks may not be the same.

Oral tivozanib has already been approved to be used for cancer in the European Union countries and the United States. The following risks are reported in the prescribing information in the United States and the European Union countries.

* Hypertension (high blood pressure)
This is the most frequent side effect after oral administration of tivozanib in cancer patients (reported in 45% of patients treated with tivozanib); approximately half of the reported hypertension was severe.
* Other important systemic risks reported in the prescribing information in the United States include:
	+ Cardiac failure (the heart is unable to pump blood around the body properly)
	+ Cardiac ischemia (the heart muscle is not getting enough blood [which contains oxygen and nutrients] to work as it should) and arterial thromboembolic events (a clot that have come from another part of the body causes a sudden interruption of blood flow to an organ or body part)
	+ Venous thromboembolic events (a condition that occurs when a blood clot forms in a vein)
	+ Bleeding events
	+ High levels of protein in the urine
	+ Thyroid dysfunction: hypothyroidism (a common condition where the thyroid does not create and release enough thyroid hormone into the bloodstream, which makes the metabolism slow down, can make you feel tired, gain weight, and be unable to tolerate cold temperatures) and hyperthyroidism (a condition in which the thyroid creates and releases more hormones than you need, which can make the metabolism speed up and could cause a rapid heartbeat, weight loss, increased appetite, and anxiety)
	+ Risk of impaired wound healing
	+ Reversible posterior leukoencephalopathy syndrome (a rare condition marked by headaches, vision problems, mental changes, seizures, and swelling in the brain. The symptoms usually come on quickly and can be serious and life threatening.)

**Risks of aflibercept**

The most common side effects include:

* Increased redness of the white part of the eye
* Eye pain
* Cataract (the eye’s natural lens becomes cloudy)
* Vitreous (gel-like substance) detachment
* Vitreous floaters (dark spots that appear to float in your vision)
* Moving spots in the field of vision
* Increased pressure in the eye
* Bleeding in the eye
* Thromboembolism (blood clots)
* Corneal erosion (changes to the eye cornea)

As with all medications, KHK4951 and aflibercept carry a risk of provoking an allergic reaction in sensitive individuals, ranging from mild to severe. Reactions could include skin rash, hives, itching, difficulty breathing, or swelling of the face, lips, tongue or throat. However, the likelihood of a severe allergic reaction is very low. If you experience any concerning symptoms while taking the investigational eye drops, inform your doctor immediately so proper treatment can be provided if needed. If you have any side effects, tell your study doctor immediately so you can receive appropriate care.

Table 1: Procedural Risks

|  |  |
| --- | --- |
| Blood samples/ dye administration into a vein | Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort, pain, and bruising, and there is a potential for infection. Other risks, although rare, include nerve damage, bleeding, dizziness and fainting.The same risks are expected for administration of dye and fluorescein into a vein in your arm. |
| Blood pressure and pulse rate | An inflatable cuff will be placed on your arm and a machine will measure your blood pressure and pulse rate, after you have taken an adequate rest. You may experience mild discomfort or pressure in your arm while the cuff is inflated. |
| Color fundus photograph | You may have some brief discomfort from the bright light, and you may “see spots” for a few minutes after pictures are taken. These will go away on their own and do not need treatment. |
| ECG | Small sticky pads are placed on your chest, shoulders and hips. These may cause some local irritation and be uncomfortable to remove. |
| Eye drops to dilate the pupil | Risks of dilation of the pupil include light sensitivity, blurry vision, trouble focusing on close objects, and stinging right after the drops are put in. |
| Fluorescein | Risks of fluorescein include: allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue; staining of soft contact lenses and yellow tears. As very rare cases, heart attack, stroke (blood clots in the brain), or even death due to fluorescein have also been reported. |
| Injection in the eye | Risks of injections in the eye include: * Pain, foreign body sensation, having watery eyes
* Bleeding (blood spot on the eye, bleeding into the thick fluid that fills the center of the eye [vitreous gel])
* Tear in the retina, retinal detachment (retinal cells separated from the layer of blood vessels that provides oxygen and nourishment to the eye)
* Cataract (clouding of the normally clear lens of the eye)
* Endophthalmitis (infection of the tissues or fluids inside the eyeball)
* Uveitis (eye inflammation that affects the middle layer of tissue in the eye wall), retinal vasculitis (inflammation of the vessels of the retina), loss of vision (from any of above), loss of the eye (from a severe infection), increased intraocular pressure with damage to eye nerve
* Need for surgery to address some of the complications above
 |
| Intraocular pressure | The device used to measure the pressure inside of the eyes could cause a scratch on the clear front surface of the eye. If the device causes a scratch, the eye may be uncomfortable until the scratch heals, which normally takes about a day and you may be treated by your study doctor. |

Information on any abnormalities discovered during your tests, even if it is not related to the study, will be communicated to you in a timely fashion. There is a risk that this may lead to additional diagnostic testing or treatments, which can be associated with various complications.

# WHAT ARE THE POSSIBLE BENEFITS?

We hope that you will be helped by taking part in this study, but we cannot guarantee this. You may get information about your health from physical examinations and medical tests carried out in this study.

It is possible that the results may not help you individually, but the information we get from this study will help us improve treatment for people like you in the future.

# ARE THERE ALTERNATIVE TREATMENTS?

You do not have to be in this study to get treatment for your DME. Instead of participating in this study, you may choose not to undergo the proposed treatment and your DME will be treated in a routine manner. Other treatments include anti-VEGF agents such as aflibercept, ranibizumab, brolucizumab, and faricimab. Bevacizumab has been approved in the United States for cancer but not for the treatment of DME; however, many doctors have been injecting it into the eye to treat DME (off‑label use). Your study doctor can discuss your treatment options with you.

# WILL I INCUR ANY EXPENSES OR RECEIVE ANY PAYMENTS?

There are no additional costs associated with taking part in this study. All medication, tests and medical care required as part of the study will be provided to you at no charge, which include all aflibercept treatments determined to be necessary by the study doctor regardless of whether it is administered to the study eye or not.

Fellow eye treatment for DME provided on the study will be according to standard of care and will start at the start of the investigational eye drops administration (the day after Week 16) to the end of the investigational eye drops administration (the day before Week 52).

You or your insurance company will have to pay for medicines that are part of your standard of care.

You will recieve $100.00 per completed visit.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid following each completed visit.

If you have any questions regarding your compensation for participation, please contact the study staff.

You may be reimbursed for any reasonable expenses for traveling, parking, meals, etc. associated with the study visits. You will be reimbursed after you submit your travel receipts to the study staff.

You may also be eligible to receive booked transportation services to and from your study visits. If you qualify for and agree to utilize such services, you will be given instructions on how to contact the third-party vendor who will provide for and arrange transportation and reimbursement services for this study. In order to provide you with transportation and reimbursement services for this study, the third-party vendor and its employees may receive your personal data, such as your name, address, and telephone number from the study site. You will be reimbursed approximately 1 week after you submit your travel receipts to the third-party vendor. Please discuss with the site staff or study doctor for more details.

The Sponsor is paying the study doctor and/or the study sitefor their work in this study*.*

The Sponsor may use the information collected from your biological samples for commercial profit. You will not get a share in this profit.

# WHAT IF I AM INJURED DURING THE STUDY?

If you experience any unexpected symptoms or injury, and if emergency medical treatment is required, please report it immediately to the study doctor at the phone number listed on page 1 of this form.

If you have a physical injury or illness directly related to the study therapy or study procedure which was properly performed in accordance with the protocol (referred to as a study-related injury), medical treatment will be provided to you. You will not be charged for this treatment. The Sponsorwill cover the cost of reasonable and necessary medical treatment for a study-related injury and has insurance to cover the study-related injury. Study-related injuries do not include injuries that result from your own fault or intention. Additionally, payment for such things as lost wages, expenses other than medical care, or pain and suffering is not available. You do not give up your legal rights by signing this form.

Note: Some personal health insurance companies may require that you inform them about participation in a study. We suggest that you contact your personal health insurance company if this is the case, to determine whether participation in the study will affect your personal health insurance.

To pay medical expenses, the sponsor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

# WHAT WILL HAPPEN IF THERE IS ANY NEW INFORMATION?

The study doctor or their staff will tell you in a timely manner if any new information becomes available for KHK4951 and/or aflibercept that may affect your decision to stay in this study (see page 1 of this consent form).

# WILL INFORMATION ABOUT ME BE KEPT CONFIDENTIAL?

Data directly identifying you (name, address, etc.) will be replaced by a combination of characters specifically assigned to you and your information by your study doctor (i.e., they are coded/encoded/key-coded/pseudonymized). Records directly identifying you by name or any other personal data/Personally Identifiable Information that may indirectly identify you will be kept confidential and will not be made publicly available. If the results of the study are published, your identity will remain confidential, where allowed by local laws and/or regulations.

The Sponsor and site will retain your records until 25 years have elapsed since the end of the study.

Your access to your health information will be limited during this study. When the study is over, you will have the right to see your health information related to this research.

Representatives of the sponsor (including those from PAREXEL International and laboratories contracted by the sponsor), the IRB, and regulatory authorities such as the FDA will be granted access to your medical records without violating your confidentiality, to the extent permitted by law. If reports or articles are written about the study, you will not be identified by name in them. While every effort will be made to protect the confidentiality of your information, absolute confidentiality cannot be guaranteed.

A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.  GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.  GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION TO USE & DISCLOSE MEDICAL INFORMATION

As part of this study, medical information about you will be collected and analyzed. This medical information will include (but is not limited to) your date of birth, gender, medical history (that is, data from your medical records such as past or present health conditions and medications, and the results of procedures and test you undergo during the study and had before the study), laboratory test results, physical exam data and data collected from the procedures described in your informed consent form for this study.

Under federal law, your medical information cannot be used or disclosed by your study doctor for research purposes unless you sign this authorization. By signing this document, you authorize the study doctor and staff to use this information in conducting the study, and to provide access to or copies of this information to Kyowa Kirin Co., PAREXEL (contract research organization conducting the study on Kyowa Kirin Co. behalf), the central laboratory, and other organizations working with Kyowa Kirin Co. to monitor the progress of the study or analyze the study data. Access to this information is necessary for Kyowa Kirin Co. to check that the study is being done correctly, and to collect and analyze data about the safety and effectiveness of the study drug.

In addition, this information may also be disclosed to the U.S. Food and Drug Administration (FDA) or similar, foreign, regulatory authorities, for the purpose of attaining regulatory approval. The information may also be disclosed to the Advarra IRB (institutional review board). The purpose of this board is to ensure that participants’ safety and rights are protected.

This authorization to use or disclose the information as described above is not time-limited (that is, will not automatically expire). In California and any other state that requires an expiration date, the Authorization will expire 50 years after you sign this authorization document.

You agree that, while the study is still in progress, you may not be given access to medical information about you that is related to the study. This may include, for example, information about whether you are receiving study drug or placebo, or any other information that is “blinded” (that is, kept secret during the study to prevent bias). While a request for access to medical information may be denied, the study doctor and staff will consider whether it’s medically appropriate under the circumstances to allow access. Your agreement that you may be denied access to your study-related medical information during the study will not be used to deny you access to that information after the study is completed at all locations and study results are analyzed.

You may decide not to sign this authorization, or you may revoke (withdraw) this authorization at any time. You can do this by writing to your study doctor at the address listed on page 1 of this form.

You can only participate in the study if you authorize the use and disclosure of the information as described above. If you decide not to sign this authorization form, you will not be enrolled in the study. If you sign this authorization and decide later to withdraw this authorization, you will not be permitted to continue your participation in the study. Information collected up to the time that you end this authorization may continue to be used and disclosed as described above, but only as necessary to protect the integrity of the research study.

You should know that, once information is disclosed under this authorization to someone who is not a health care provider, the information is no longer protected by federal law. The Sponsor and those working with the Sponsor on this study (such as PAREXEL) will only use and disclose your information as described in this Authorization. If reports or articles are written about the study, you will not be identified by name in them.

You will be given a copy of this authorization after you have signed and dated it.

**STATEMENT OF AUTHORIZATION**

I confirm that I have read the statements in the HIPAA Authorization for this study. I confirm that the information has been explained to me. I agree to participate in this study, with the understanding that I am authorizing the use and disclosure of the information as described above.

I understand that I will receive a signed and dated copy of this Authorization for my records.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Participant’s Printed Name

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_

Participant’s Signature Date

**WITNESS SIGNATURE FOR PARTICIPANTS WHO CANNOT READ** (if applicable)

The study participant has indicated that he/she is unable to read. This Authorization document has been read to the participant by a member of the study staff, discussed with the participant by a member of the study staff, and the participant has been given an opportunity to ask questions of the study staff.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Printed Name of Impartial Witness

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_

Signature of Impartial Witness Date

# WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

* Whom to contact in the case of a research-related injury or illness;
* Payment or compensation for being in the study, if any;
* Your responsibilities as a research participant;
* Eligibility to participate in the study;
* The study doctor’s or study site’s decision to withdraw you from participation;
* Results of tests and/or procedures;

**Please contact the study doctor at the telephone number listed on the first page of this consent document.**

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

* By **mail**:

Study Subject Adviser

Advarra IRB

6100 Merriweather Dr., Suite 600

Columbia, MD 21044

* or call **toll free**:    877-992-4724
* or by **email**:          adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00074303.

# CONSENT STATEMENT OF PARTICIPANT

Study title: A Phase 2, Multicenter, Randomized, Double-Masked, Parallel-Group Study to Assess the Efficacy and Safety of KHK4951, a Vascular Endothelial Growth Factor Receptor Inhibitor, in Patients with Diabetic Macular Edema

* I have received a verbal description of the above study and have read the written information in the main consent form and supplementary information sheets. I have been given the chance to discuss the study and ask questions.
* I voluntarily consent to participate in this study, including all assessments, to document and record **all** procedures including lifestyle restrictions, birth control requirements, and taking of blood and urine samples.
* I understand that I am free to withdraw at any time. I understand that if I choose to not participate or to withdraw, my current medical care will not be affected by this decision.
* I agree that my primary physician or family doctor may be told of my participation in this study.
* I agree that my personal data, including data relating to my physical or mental health, and race and ethnic origin, may be used as described in this consent form. Where available, my medical records may be accessed directly, off-site access if required, to the extent permitted by laws/regulations, without violating my confidentiality.
* I agree and authorize that my **coded personal data** may be transferred within and outside the United States to countries where personal data may not have the same level of statutory protection as in the United States.
* I agree and authorize that samples collected from me for the purposes described in this consent form will be processed in coded form within and outside the United States where personal data may not have the same level of statutory protection as in the United States, by the Sponsor, its affiliates, representatives and collaborators for scientific and regulatory purposes and that the remainder of the samples collected to check the levels of KHK4951 in your blood will be stored for future research up to 15 years from the date of completion of the scheduled assessments of the last participant in this study. Remaining samples after the completion of the final report will be discarded as soon as they are no longer required.
* I understand that I will get and may keep a copy of this signed and dated consent form for my record.
* By signing and dating this consent form, I have not given up any of the legal rights that I would have if I were not a participant in a medical research study.

|  |  |  |
| --- | --- | --- |
|  |  |  |
| Signature of Participant | Date (mm/dd/yyyy) | Printed Name of Participant |
|  |

**WITNESS SIGNATURE FOR PARTICIPANTS WHO CANNOT READ (if applicable)**

The study participant has indicated that he/she is unable to read. The consent document has been read to the participant by a member of the study staff, discussed with the participant by a member of the study staff, and the participant has been given an opportunity to ask questions of the study staff.

|  |  |  |
| --- | --- | --- |
|  |  |  |
| Signature of Witness | Date (mm/dd/yyyy) | Printed Name of Witness |

# STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

I, the undersigned, certify that to the best of my knowledge, the participant signing this consent form had the study fully and carefully explained and clearly understands the nature, risks, and benefits of participation in this study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| Signature of Investigator (or Other Authorized Person Obtaining Consent) |  | Date (mm/dd/yyyy) |  | Printed Name of Authorized Person Obtaining Consent |

# Supplementary Information Sheet 1: Glossary of Terms

|  |
| --- |
| Study personnel: |
| **Sponsor** | A person, company, institution, group, or organization that oversees or pays for a clinical study and collects and analyzes the data. |
| Study design terms: |
| **Double-masked** | This means that neither the Sponsor nor the study doctor knows what treatment you are taking. You also will not know what treatment you are taking. The reason for this is so that there is no influence on the collection of safety or effectiveness information on KHK4951. |
| **Randomized** | If you take part in the study, a computer will randomly allocate you to a treatment arm (like flipping a coin or throwing a die). This allows a fair comparison between the treatment arms to see whether there are different results between these arms. |
| **Study** | ‘Study’ is another name for a clinical research trial. |
| Treatments: |
| **Placebo** | A placebo is an inactive substance or sham treatment which is designed to have no therapeutic value. |
| **Study treatment** | Term used for treatment with investigational eye drops and/or aflibercept during the study. |
| Assessments/Procedures: The study doctor will explain these procedures to you beforehand. |
| **Best-corrected visual acuity** | This is an assessment to test your vision using the Early Treatment Diabetic Retinopathy Study visual acuity chart. You will read letters from a specific distance away from the chart. |
| **Color fundus photography** | This imaging test is used to evaluate structures in the eye using a camera or other equipment. Color photographs of the eye will be taken. |
| **Dilated fundus examination/indirect ophthalmoscopy** | Dilated fundus examination is a diagnostic procedure that employs the use of eye drops to dilate or enlarge the pupil (the circular black area in the center of an eye). It allows a better view of the fundus of the eye (back part of the eye).Indirect ophthalmoscopy is a diagnostic procedure used to examine the retina (inner lining of the eye that generates vision) and optic nerve. Indirect ophthalmoscopy is a non-invasive procedure that uses a handheld lens and a light source to magnify the back of the eye. It is a common procedure used to diagnose and monitor retina diseases. |
| **Electrocardiogram (ECG)** | ECG (or heart trace): the electrical activity of your heart will be measured. |
| **Fluorescein angiography** | This is an imaging test to take special pictures of the blood vessels in your eye.During the test, you will receive eye drops that dilate the pupil (the circular black area in the center of an eye), and a dye called fluorescein to highlight the blood vessels in your retina is injected into a vein in your arm. |
| **Fluorescein staining of the cornea** | Fluorescein is a brightly colored dye to check the surface of the eye for scratches. |
| **Follow-up period** | The final part of a study where participants are checked for any safety concerns following the study treatment. |
| **Intraocular pressure** | Pressure of the fluid inside of the eyes. This assessment will be done with a device called tonometry that measures the pressure inside of the eyes by flattening the cornea (clear part at the front of the eye). |
| **Iris transillumination** | This is a medical examination used to visualize the iris (colored part) of the eye. This assessment can be used to evaluate the integrity and characteristics of the iris. |
| **Run-in period** | This is a period between the enrollment and randomization phases of a study when all participants receive the same treatment. |
| **Screening period** | This is the initial part of every study where potential participants are checked to make sure that they meet the criteria for the study (e.g., have the right illness, laboratory parameters, or are the right age group) and are also safe to take part. |
| **Slit-lamp examination of the anterior segment** | The eye is examined using a microscope with a high‑intensity light source mounted to a table. The study doctor can check the anterior part of the eye and inner eye for any problems using bright light and a magnifying lens. |
| **Spectral domain-optical coherence tomography (****SD-OCT)** | This is a quick, painless, non-invasive imaging procedure that scans the inside of your eye. This assessment helps in the diagnosis and monitoring of various retina and optic nerve conditions. |
| **Specular microscopy** | This is a non-invasive imaging technique use to examine the corneal endothelium, which is the innermost layer of the cornea. |
| **Treatment period** | The part of the study where you will receive the study treatment. |
| Other: |
| **Coded personal data** | Your data collected at the study site with your name and contact details will be replaced by a code by the study doctor. The study doctor will keep the link between your name/contact details and the code to ensure your safety and confidentiality.Coded information cannot identify you unless your study doctor provides your name or contact details, where allowed by applicable law. |

# Supplementary Information Sheet 2: Assessments

Table 2: Study Assessments/Procedures

| Study assessments/procedures | Screening period | Run-in period | Study Treatment Period | Follow‑up period |
| --- | --- | --- | --- | --- |
| Visit to the study site | 1a | 2 | 3 | 4 | 5 | 6 | No visit | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Week |  | 0 | 4 | 8 | 12 | 16 | 16+1 day | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 |
| Day | Within 30 days before first aflibercept injection | 1 | 29 | 57 | 85 | 113 | 114 | 141 | 169 | 197 | 225 | 253 | 281 | 309 | 337 | 365 | 393b |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographic information, medical history, smoking history, urine pregnancy test (only for women who can get pregnant), height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Eligibility assessment by the study doctor | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  |
| Electrocardiogram | X |  |  |  |  | X |  |  |  |  |  |  |  |  |  | X |  |
| Interview by the study doctor about your vision‑related functioning and vision‑related quality of life | X |  |  |  |  | X |  | X |  |  | X |  |  | X |  | X |  |
| Blood and urine tests to check your overall well‑being | X |  |  |  | X | X |  | X |  |  | X |  |  | X |  | X |  |
| Blood tests to check the levels of KHK4951 in your blood |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  | X | Xc |
| Physical examination | X | X | X | X | X | X |  | X | X | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X |  | X | X | X | X | X | X | X | X | X |  |
| Side effects, concomitant medications and therapies | Continuously assessed |
| Iris transillumination | OU |  |  |  |  | OU |  |  |  |  |  |  |  |  |  | OU |  |
| Specular microscopyd | OU |  |  |  |  | OU |  |  |  |  |  | OU |  |  |  | OU |  |
| Fluorescein angiography | OUe |  |  |  |  | OU |  |  | OU |  |  | OU |  |  |  | OU |  |
| Color fundus photography  | OU |  |  |  |  | OU |  | SE | OU | SE | SE | OU | SE | SE | SE | OU |  |
| Intraocular pressure | OU | SEf | SEf | SEf | SEf | OUf |  | SEg | OUg | SEg | SEg | OUg | SEg | SEg | SEg | OUg |  |
| Slit-lamp examination of the anterior segment | OU | SEf | SEf | SEf | SEf | OUf |  | SEg | OUg | SEg | SEg | OUg | SEg | SEg | SEg | OUg |  |
| Fluorescein staining of cornea, dilated fundus examination/indirect ophthalmoscopy, best-corrected visual acuity, spectral domain‑optical coherence tomography | OU | SE | SE | SE | SE | OU |  | SE | OU | SE | SE | OU | SE | SE | SE | OU |  |
| Aflibercept injection |  | Xh | X | X | X | Xi |  | You may receive aflibercept injections as rescue treatment if deemed necessary by the study doctor. |  |
| Assignment to one of the study treatment arms |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |
| Administration of investigational eye drops |  |  |  |  |  |  | Twice a day (morning and evening) from Day 114 until one day prior to Day 365 visit |  |  |

a: Screening period may have multiple visits to the study site.

b: Up to four weeks after the end of study treatment or before you initiate new therapy after the last study treatment, whichever comes first. The assessments will be performed at the study site or via phone call, depending on the study status and the study doctor’s discretion.

c: If the follow-up visit is conducted via phone call, this assessment will not be performed.

d: This assessment will be performed at selected study sites only. Therefore, you may not undergo this assessment.

e: Images from previous eye examinations (fluorescein angiography) may be used as part of your screening examinations as long as they were performed within 30 days of the date of first aflibercept injection.

f: This assessment will be done twice, before and after aflibercept injection. At the second examination after aflibercept injection, the examination will be done only in the injected eyes.

g: If you receive aflibercept injection as rescue treatment, these assessments will be done to the injected study eye after aflibercept injection in addition to the scheduled assessments.

h: You may receive a follow-up call about 2 days after the first aflibercept injection. Please contact the study site at any time if you have any health‑related concerns. If warranted, you will be asked to visit the study site as soon as possible for safety assessments.

i: You will receive the fifth injection of aflibercept only when the study doctor confirms that you responded to the first four injections of aflibercept. If you do not meet the study’s predefined criteria, the fifth injection of aflibercept will be optional.

OU=both eyes, SE=study eye