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Study of the safety, tolerability, processing by the body, and ability to provoke immune system response of ocular injections of RO7446603 alone and in combination with aflibercept or faricimab in participants with diabetic macular edema

Submission date	**Recruitment status**	[X] Prospectively registered
17/06/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
20/06/2022	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
04/12/2023	Eye Diseases	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Diabetic macular edema (DME) is a serious eye condition that affects people with high blood sugar. DME results when the damaged blood vessels leak fluid and cause swelling, which blurs vision. If it worsens, the eye may begin to form new, abnormal blood vessels over the light-sensitive layers of nerve tissue at the back of the eye (retina), which can break easily and bleed, causing severe vision loss and even blindness. The development of a mode of treatment called anti-vascular endothelial growth factor (anti-VEGF) pharmacotherapy (medication) in the past 10 years has led to dramatic improvements in visual outcomes for patients with DME. RO7446603 may lead to stabilization of the diseased blood vessels and improve visual and structural (anatomical) outcomes in DME compared with previous treatments. RO7446603 is an experimental drug. Health authorities have not yet approved RO7446603 for the treatment of DME or any other disease. The main aims of this study are to evaluate how safe RO7446603 is at different doses and to understand the way the body processes the drug, and to test RO7446603 when given with aflibercept (Eylea®), or faricimab (Vabysmo) a standard approved treatment for patients with DME.

Who can participate?
People aged 18 years or more with DME

What does the study involve?
Participants will need to be a part of this study for about 9 months depending on the group the participant is assigned to. The study will include the following periods:
1. A screening period of up to 28 days to check the eligibility of participants for stage 1-4 and an additional enrichment screening period of 28-33 days for stage 4 only.

2. A treatment period of up to 16 weeks for participants in groups 1 and 28 weeks for participants in groups 2, 3 and 4, where participants will receive single or multiple injections of RO7446603 in the eye, with or without aflibercept or faricimab.
3. A follow-up period during which participants will have check-up visits with the study team either at the clinic or via telephone
The study will be conducted in four stages:
1. A single ascending dose stage, where participants will receive RO7446603 given as one single injection in the eye
2. A multiple-dose monotherapy stage, where participants will receive RO7446603, given as two injections in the eye 8 weeks apart
3. A multiple-dose co-administration with aflibercept stage, where participants receive RO7446603 given as two injections in the eye 8 weeks apart, along with four injections of aflibercept 4 weeks apart, in accordance with the approved drug label.
4. A multiple-dose co-administration with faricimab stage, where participants receive faricimab given as a single injection in the eye during the run-in treatment which is followed by enrichment screening. If participants are eligible to participate in the study, they will then receive either RO7446603 and faricimab or faricimab alone.
– RO7446603 will be given as two injections into the eye 8 weeks apart, along with three injections of faricimab 4 weeks apart.
– Faricimab will be given as three injections into the eye 4 weeks apart.

During this study, participants will have to visit the clinic 10–12 times, depending on the group to which they are assigned. Visits may last for 1–5 hours.

What are the possible benefits and risks of participating?
The participants' health may or may not improve in this study, but the information collected may help other people who have a similar medical condition in the future. Participants may have a side effect from the drugs (RO7446603, aflibercept, and faricimab) or procedures used in this study. These can be mild to severe and even life-threatening, and they can vary from person to person.

Risks associated with RO7446603 include infection inside the eye, inflammation inside the eye, an immune or allergic response against the drug, and an increase or decrease in blood pressure.

Risks associated with aflibercept:
Important side effects: reduced vision, bloodshot eye (caused by bleeding of the membrane covering the white of the eye), eye pain, infection inside the eye, inflammation inside the eye, cloudiness of the lens of the eye (cataracts), detachment or tear of the retina (which may progress to cause a loss of vision), increase in fluid pressure inside the eye, blood clots blocking blood vessels, which may lead to stroke or heart attack, an immune response against the drug.
Very common side effects: a decrease in vision, bleeding in the back of the eye (retinal hemorrhage), bleeding on the surface of the front of the eye (conjunctival hemorrhage), eye pain.
Common side effects: separation of one of the layers in the back of the eye (retinal pigment epithelium detachment or tear), bleeding in the eye (vitreous hemorrhage), temporary increase in intraocular pressure (fluid pressure inside the eye), blurred vision, injection site pain, feeling that there is something in the eye (foreign body sensation in eyes), bleeding at the site of the injection, inflammation on the surface of the eye (punctate keratitis), degeneration of the back of the eye (retinal degeneration), clouding of the lens in the eye (cataract), damage to the front window of the eye (corneal erosion, corneal abrasion), small particles or spots in vision (vitreous floaters), separation of the vitreous humor from the back of the eye (vitreous detachment), increased tear production, swelling of the eyelids (eyelid edema), eye redness (conjunctival

hyperemia)
Uncommon side effects: allergic reactions, inflammation of the internal parts of the eye (anterior chamber flare, uveitis, iritis, iridocyclitis), swelling and deposits in the front window of the eye (corneal edema), abnormal sensation in the eye, injection site irritation, infections inside the eye (endophthalmitis), retinal tear (formation of a small hole in the retina or detachment (separation of the retina from the back of the eye), clouding of the lens (lenticular opacities), damage to the front layer of the eye (corneal epithelium defect), eyelid irritation
Rare side effects: blindness, clouding of the lens in the eye due to trauma/injury (traumatic cataract), inflammation in the jelly-like filling of the eye (vitritis), collection of pus in the eye (hypopyon)
Participants may develop increased pressure within the eye when a medication is injected into the eye. Participants with a history of glaucoma may be at more risk with RO7446603.
Participants receiving injections of medications into their eye have developed infections inside and/or outside the eye (endophthalmitis and/or periocular, and/or corneal infections), retinal detachment (separation of the retina from the underlying tissue), or cataracts (cloudiness of the eye lens). Some participants can also develop bleeding inside the eye. Participants may experience blurred vision for a period of time after the injection itself. Participants should not drive or use machinery until this has resolved.
Ocular fluid samples will be collected from the front part of the participant's eye using a small needle. Participants may experience a temporary decrease in pressure after aqueous humor collection. While rare, aqueous humor collection can cause eyes to develop infections inside and /or outside the eye (endophthalmitis, periocular, and/or corneal infections) or cataracts (cloudiness of the eye lens). Some participants can also develop bleeding inside the eye. Participants may experience blurred vision for a period of time after the procedure itself. Participants should not drive or use machinery until this has resolved.
Fluorescein angiography photographs (special pictures taken of the eyes to determine the extent of macular edema or swelling) require an injection of a dye into a vein in the participant’s arm. This may cause some discomfort at the needle site, and the injection of the dye could irritate the vein, or cause redness, swelling or redness at the injection site. It is possible that the vein or the skin around the site could be damaged. The most common side effects of the dyes are nausea and vomiting, and occasionally allergic reactions or feeling faint. The dye may also stain skin and urine, although this will only last for about a day. In rare cases, allergic reactions can be serious and include swelling of the voice box, difficulty breathing, and heart stopping (cardiac arrest).
Potential risks with dilation of the eyes are nausea, vomiting, dryness of the mouth, flushing, dizziness for a short time; allergic reaction; and sudden increase in pressure inside the eyeball.

Risks associated with faricimab:
Bleeding of the mucous membrane covering the white of the eye and inner lid (conjunctival hemorrhage), moving spots or dark shapes in your vision (Vitreous floaters), increase in fluid pressure inside the eye (temporary increase in intraocular pressure), eye pain, irritation, redness, discomfort or itching, increased production of tears, scratched cornea, damage to the clear layer of the eyeball that covers the iris, blurred vision, swelling of the gel-like substance inside the eye (vitritis), swelling in the iris and its adjacent tissue in the eye (iritis, iridocyclitis, uveitis), foreign body sensation in the eye, endophthalmitis (serious inflammation or infection inside the eye), temporary decrease in vision, tearing of the layer at the back of the eye that detects light (the retina) and separation of the retina from the underlying pigment cell layer (retinal detachment).
There may be a risk in exposing an unborn child to the study drug, and all risks are not known at this time. Women and men must take precautions to avoid exposing an unborn child to the study drug. Participants who are pregnant, become pregnant or are currently breastfeeding cannot take part in this study.

Where is the study run from?
Genentech, Inc. (Switzerland)

When is the study starting and how long is it expected to run for?
January 2022 to September 2024

Who is funding the study?
Genentech, Inc. (Switzerland)

Who is the main contact?
global-roche-genentech-trials@gene.com

Contact information

Type(s)
Public

Contact name
Dr Clinical Trials

Contact details
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Grenzacherstrasse 124
Basel
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CH-4070
+1 (0)888 662 6728
global-roche-genentech-trials@gene.com

Additional identifiers

Protocol serial number
GR43828

Study information

Scientific Title
A Phase I, multicenter, open-label study of the safety, tolerability, pharmacokinetics, and immunogenicity of intravitreal injections of RO7446603 alone and co-administered with aflibercept or faricimab in patients with diabetic macular edema

Study objectives
Current study hypothesis as of 08/08/2023: :

The aim of the study is to investigate the ocular and systemic safety and tolerability of RO7446603 following single and multiple intravitreal (ITV) doses, as monotherapy, or co-administered with ITV aflibercept or faricimab, in participants with diabetic macular edema (DME).

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Previous study hypothesis:

The aim of the study is to investigate the ocular and systemic safety and tolerability of RO7446603 following single and multiple intravitreal (ITV) administrations, with or without ITV aflibercept, in participants with diabetic macular edema (DME).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/03/2022, Advarra (6100 Merryweather Dr., Suite 600, Columbia, MD 21044, USA; +1 (0)410 884 2900; contact@advarra.com), ref: Pro00062159

Primary study design
Interventional

Study design
Current study design as of 08/08/2023:

Phase I open-label multi-center interventional study. The study consists of four parts: a single ascending dose (SAD) stage (Part 1), a multiple-dose (MD) monotherapy stage (Part 2), a MD stage where RO7446603 will be co-administered with aflibercept (Part 3) and MD stage where RO7446603 will be co-administered with faricimab (Part 4)

Previous study design:

Phase I open-label multi-center interventional study. The study consists of three parts: a single ascending dose (SAD) stage (Part 1), a multiple-dose (MD) monotherapy stage (Part 2), and a MD stage where RO7446603 will be co-administered with aflibercept (Part 3)

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Diabetic macular edema (DME)

Interventions
Current interventions as of 08/08/2023:

Part 1 Single Ascending Dose (SAD): Participants, in multiple cohorts, will receive a single dose of RO7446603, as ITV injection on Day 1, as guided by specific clinical criteria for dose escalation.

Part 2 Multiple-Dose (MD) Monotherapy: Participants, in multiple cohorts, will receive four different dose levels of RO7446603 (two doses at each planned dose level), as ITV injection every 8 weeks (Q8W) as guided by specific clinical criteria for dose escalation.

Part 3 MD Co-Administration with Aflibercept: Participants will receive two different dose levels of RO7446603 (two doses at each planned dose level) as ITV injection, Q8W, along with four injections of aflibercept every 4 weeks (Q4W), in accordance with the approved drug label.

Part 4 MD Co-Administration with Faricimab: Participants will receive single dose of faricimab during the run-in treatment and after an enrichment screening period. Eligible participants will be randomized in a 1:1:1 ratio to receive two dose of RO7446603 at one of the two dose levels planned (dose to be decided) as ITV injection, Q8W, co-administered with three doses of faricimab, ITV injection Q4W or will receive only three doses of faricimab, Q4W as the control group in accordance with the approved drug label.

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Previous interventions as of 10/03/2023:

Part 1 Single Ascending Dose (SAD): Participants, in multiple cohorts, will receive a single dose of RO7446603, as ITV injection on Day 1, as guided by specific clinical criteria for dose escalation.

Part 2 Multiple-Dose (MD) Monotherapy: Participants, in multiple cohorts, will receive two doses of RO7446603, as ITV injection every 8 weeks (Q8W) as guided by specific clinical criteria for dose escalation.

Part 3 MD Co-Administration: Participants will receive two different dose levels of RO7446603 (two doses at each planned dose level) as ITV injection, Q8W, along with four injections of aflibercept every 4 weeks (Q4W), in accordance with the approved drug label.

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Part 2 Multiple-Dose (MD) Monotherapy: Participants, in multiple cohorts, will receive two doses of RO7446603, as ITV injection every 8 weeks (Q8W) as guided by specific clinical criteria for dose escalation.

Part 3 MD Co-Administration: Participants will receive two doses of RO7446603 as ITV injection, Q8W, followed by four doses of aflibercept ITV injection every 4 weeks (Q4W).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO7446603

Primary outcome(s)
Current primary outcome measure as of 08/08/2023:

1. Percentage of participants with adverse events (AEs) from day 1 up to end of treatment or early termination visit (up to approximately 36 weeks)
2. Percentage of participants with severity of AEs determined according to Division of AIDS

(DAIDS) table for grading the severity of adult and pediatric adverse events (HHS 2017) from day 1 up to end of treatment or early termination visit (up to approximately 36 weeks)
3. Number of participants with ocular AEs from day 1 up to end of treatment or early termination visit (up to approximately 36 weeks)
4. Number of participants with abnormal laboratory findings measured using blood and urine samples from screening up to end of treatment or early termination visit (up to approximately 36 weeks)
5. Number of participants with abnormal physical findings assessed by evaluation of the head, eyes, ears, nose, and throat, and measurement of height and weight from screening up to end of treatment or early termination visit (up to approximately 36 weeks)
6. Number of participants with abnormal vital signs assessed by measurement of temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure from screening up to the end of treatment or early termination visit (up to approximately 36 weeks)
7. Number of participants with abnormal electrocardiogram (ECG) parameters measured using a standard high-quality, high-fidelity digital electrocardiograph machine from day 1 up to 8 weeks after last dose of study drug (up to approximately week 16)
8. Changes from baseline in Best-Corrected Visual Acuity (BCVA) score measured using a set of three Precision Vision™ or Lighthouse distance acuity charts from screening up to end of treatment or early termination visit (up to approximately 36 weeks)

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Previous primary outcome measures as of 10/03/2023:

1. Percentage of participants with adverse events (AEs) from day 1 up to end of treatment or early termination visit (up to approximately 20 weeks)
2. Percentage of participants with severity of AEs determined according to Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events (HHS 2017) from day 1 up to end of treatment or early termination visit (up to approximately 20 weeks)
3. Number of participants with ocular AEs from day 1 up to end of treatment or early termination visit (up to approximately 20 weeks)
4. Number of participants with abnormal laboratory findings measured using blood and urine samples from screening up to end of treatment or early termination visit (up to approximately 20 weeks)
5. Number of participants with abnormal physical findings assessed by evaluation of the head, eyes, ears, nose, and throat, and measurement of height and weight from screening up to end of treatment or early termination visit (up to approximately 20 weeks)
6. Number of participants with abnormal vital signs assessed by measurement of temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure from screening up to the end of treatment or early termination visit (up to approximately 20 weeks)
7. Number of participants with abnormal electrocardiogram (ECG) parameters measured using a standard high-quality, high-fidelity digital electrocardiograph machine from day 1 up to 8 weeks after last dose of study drug (up to approximately week 16)
8. Changes from baseline in Best-Corrected Visual Acuity (BCVA) score measured using a set of three Precision Vision™ or Lighthouse distance acuity charts from screening up to end of treatment or early termination visit (up to approximately 20 weeks)

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Previous primary outcome measures:

1. Percentage of participants with adverse events (AEs) from day 1 up to end of treatment or early termination visit (up to approximately 2 years)
2. Percentage of participants with severity of AEs determined according to Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events (HHS 2017) from day 1 up to end of treatment or early termination visit (up to approximately 2 years)
3. Number of participants with ocular AEs from day 1 up to end of treatment or early termination visit (up to approximately 2 years)
4. Number of participants with abnormal laboratory findings measured using blood and urine samples from screening up to end of treatment or early termination visit (up to approximately 2 years)
5. Number of participants with abnormal physical findings assessed by evaluation of the head, eyes, ears, nose, and throat, and measurement of height and weight from screening up to end of treatment or early termination visit (up to approximately 2 years)
6. Number of participants with abnormal vital signs assessed by measurement of temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure from screening up to the end of treatment or early termination visit (up to approximately 2 years)
7. Number of participants with abnormal electrocardiogram (ECG) parameters measured using a standard high-quality, high-fidelity digital electrocardiograph machine from day 1 up to 8 weeks after last dose of study drug (up to approximately week 16)
8. Changes from baseline in Best-Corrected Visual Acuity (BCVA) score measured using a set of three Precision Vision™ or Lighthouse distance acuity charts from screening up to end of treatment or early termination visit (up to approximately 2 years)

Key secondary outcome(s)
There are no secondary outcome measures

Completion date
29/09/2024

Eligibility

Key inclusion criteria
1. Age ≥18 years at the time of signing the Informed Consent Form
2. Documented diagnosis of diabetes mellitus (Type 1 or Type 2)
3. Macular thickening secondary to DME involving the center of the fovea
4. Decreased visual acuity attributable primarily to DME

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex

All

Key exclusion criteria
Current exclusion criteria as of 08/08/2023:

1. Currently untreated diabetes mellitus or previously untreated participants who initiated oral anti-diabetic medication or insulin within 3 months prior to Day 1
2. Uncontrolled blood pressure (BP), defined as systolic >180 millimetres of mercury (mmHg) and /or diastolic >100 mmHg while the participants is at rest
3. Pregnancy or breastfeeding, or intention to become pregnant during the study
4. Participants with ITV anti-VEGF treatment within 3 months prior to Day 1
5. Participants with any ITV or periocular (subtenon) corticosteroid treatment within 6 months prior to Day 1
6. High-risk proliferative diabetic retinopathy (PDR) in the study eye
7. Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision
8. Active or history of uveitis, vitritis (grade trace or above), and/or scleritis in either eye
9. Other protocol-specified inclusion/exclusion criteria may apply

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1. Currently untreated diabetes mellitus or previously untreated participants who initiated oral anti-diabetic medication or insulin within 3 months prior to Day 1
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8. Active or history of uveitis, vitritis (grade trace or above), and/or scleritis in either eye
9. Other protocol-specified inclusion/exclusion criteria may apply

Date of first enrolment
22/06/2022

Date of final enrolment
17/03/2024

Locations

Countries of recruitment
United States of America

Study participating centre

University Retina and Macula Associates, PC
United States of America
60439-7421

Study participating centre
Retinal Consultants Medical Group Inc
United States of America
95825-8340

Study participating centre
Duke University Medical Center
United States of America
27713

Study participating centre
Retinal Consultants of Arizona
United States of America
85053-4000

Study participating centre
Associated Retinal Consultants PC
United States of America
85020-5505

Study participating centre
Austin Retina Associates
United States of America
78705-1169

Study participating centre
Valley Retina Institute PA
United States of America
78503-1518

Study participating centre

Western Carolina Retinal Associate PA
United States of America
28803-2493

Study participating centre
Charles Retina Institute
United States of America
38138-2405

Study participating centre
Cumberland Valley Retina Consultants PC
United States of America
21740-5940

Study participating centre
Retina Research Institute of Texas
United States of America
79606-1224

Study participating centre
Barnet Dulaney Perkins Eye Center
United States of America
85016-4701

Study participating centre
Blue Ocean Clinical Research
United States of America
33761-2046

Study participating centre
Cascade Medical Research Institute
United States of America
97477-1025

Study participating centre

Emanuelli Research & Development Center LLC
United States of America
00612

Study participating centre
Wagner Kapoor Institute
United States of America
23502-3933

Study participating centre
Georgia Retina PC
United States of America
30060-1137

Study participating centre
Johns Hopkins Hospital
United States of America
21287-0005

Study participating centre
The Retina Partners
United States of America
91436-2018

Study participating centre
Brown Retina Institute
United States of America
78251-4551

Study participating centre
Retina & Vitreous of Texas, PLLC
United States of America
77025-1716

Study participating centre

Palmetto Retina Center - West Columbia
United States of America
29169-2429

Study participating centre
Medical Center Ophthalmology Associates
United States of America
78240-1502

Study participating centre
Sierra Eye Associates
United States of America
89502-1605

Study participating centre
National Ophthalmic Research Institute
United States of America
33912-7125

Study participating centre
Texas Retina Associates - Dallas
United States of America
75231-5078

Study participating centre
Austin Clinical Research, LLC
United States of America
78750-2298

Study participating centre
Raj K. Maturi, MD, PC
United States of America
46290-1167

Study participating centre

Retina Consultants of Texas - The Woodlands
United States of America
77384- 4167

Study participating centre
Strategic Clinical
United States of America
76087

Study participating centre
Valley Retina Institute P.A.
United States of America
78550

Study participating centre
Barnet Dulaney Perkins Eye Center
United States of America
85206

Study participating centre
Associated Retinal Consultants PC
United States of America
48073

Sponsor information

Organisation
Genentech, Inc.

Funder(s)

Funder type
Industry

Funder Name
Genentech

Alternative Name(s)
Genentech, Inc., Genentech USA, Inc., Genentech USA

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes