Final Study Report

Study Title: Longterm efficiency and safety of intravitreal injections with bevacizumab in patients with neovascularisation or macular edema.

EU reference number: 2013-005056-15

Clinical Investigation identification number (CIV ID): N/A

Study protocol/CIP code: N/A

Investigational device / medicinal product: Bevacizumab

ClinicalTrials.gov identifier: NCT03211741

Sponsor: *Ghent University or Ghent University Hospital*

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National Coordinator/ Coordinating Investigator: Dr. Julie De Zaeytijd

Funder: N/A

Author: Dr. Julie De Zaeytijd

Date of report: 15/04/2025

By signing this final study report, I acknowledge that the information is accurate and complete.

Name and signature Coordinating Investigator: .....DE ZAEYTIJD JULIE.....

Date signature Coordinating Investigator: 15/04/2025

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1. Introduction

The advent of vascular endothelial growth factor (VEGF) inhibitors, such as ranibizumab and bevacizumab, has revolutionized the field of ophthalmology. Bevacizumab, originally developed and approved for the treatment of metastatic colorectal cancer, is not licensed for ocular use. Nonetheless, it is widely administered off-label for a growing range of retinal diseases. For many years, the lack of high-quality evidence regarding its safety and efficacy in ophthalmic use remained a concern. This gap has since been addressed by several large randomized controlled trials—namely the IVAN, CATT, and GEFAL studies—which have demonstrated comparable efficacy and safety of bevacizumab relative to ranibizumab when used intravitreally.

Choroidal neovascularization and chronic macular edema are among the most serious retinal disorders affecting the fovea. Prior to the introduction of anti-VEGF therapies, these conditions frequently led to irreversible vision loss and legal blindness. Central visual acuity loss significantly impairs daily life, affecting activities such as reading, driving, watching television, and recognizing faces. It is now well-established that VEGF plays a central role in the pathogenesis of these conditions. Inhibiting VEGF activity has proven to be an effective therapeutic strategy.

Ranibizumab and aflibercept have been approved by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of neovascular age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME). Bevacizumab, despite lacking ophthalmic approval, began to be used intravitreally after pioneering work by Philip Rosenfeld at the University of Miami, who noted its promising effects on neovascular AMD. Initial anecdotal successes quickly led to widespread global adoption of off-label intravitreal bevacizumab within six months of its introduction.

Recent head-to-head studies comparing bevacizumab to ranibizumab have confirmed that both agents offer similar outcomes in terms of safety and efficacy when used for intravitreal treatment. These findings are especially significant given the high cost of ranibizumab and aflibercept, which require frequent, often monthly, injections over extended periods. In contrast, bevacizumab is substantially more affordable, enabling access to treatment for a broader population, including patients who do not qualify (or no longer qualify) for reimbursement of licensed anti-VEGF therapies.

Despite the robust evidence from phase 3 clinical trials, there remains limited documentation of the long-term safety and efficacy of bevacizumab in routine clinical practice, particularly across diverse populations and treatment settings.

Objective

This study aims to evaluate the long-term safety and efficacy of intravitreal bevacizumab in real-world clinical practice. We will assess best-corrected visual acuity (BCVA), monitor for ocular and systemic side effects, and measure central retinal thickness using optical coherence tomography (OCT), where available. By comparing these real-world outcomes with those reported in large clinical trials, we hope to refine and optimize our treatment protocols to better serve our patient population.

2. Objectives of the study

This trial will study the use of bevacizumab in our centre, the Ghent University Hospital. Describing treatment patterns in the different pathological conditions in the “real life setting” will allow us to compare these results with known results from RCTs. It will guide us to improve our decision-making process.

2.1 Primary objectives

- Evaluating the safety of intravitreal injections with bevacizumab in patients with neovascularization or macular oedema in a real-life clinical setting.

2.2 Secondary objectives

- Evaluating the efficacy of intravitreal injections with bevacizumab in patients with neovascularization or macular oedema in a real-life clinical setting.

3. Investigational Medicinal Product

3.1 Composition and dosing

Commercially acquired bevacizumab is repackaged in an aseptic filling facility.

Bevacizumab is commonly used in a dose of 1.25mg/0.05 mL. The rationale for its use at this dose is that the molar concentration achieve after intravitreal injection is highly similar to that achieved by the 0.5 mg dose of ranibizumab. A dose escalation study found no systemic or ocular serious adverse events following a single injection of 1.0, 1.5 or 2.0 mg of bevacizumab.

3.2 Producer

N.V. Roche S.A.

Dantestraat 75

1070 Brussel

+32 2 5258211

+32 2 5258201

http://www.roche.be

3.3 Packaging

Commercially acquired bevacizumab is repackaged in an aseptic filling facility in the Pharmacy of the Ghent University Hospital. A 2-cc disposable syringe filled with 2.5mg/0.1mL bevacizumab will be used.

3.4 Administration way

Bevacizumab 1.25mg/0.05 mL will be injected intravitreally using one 30-gauge x 1/2-inch injection needle vials are for single eye use only.

3.5 Labelling

The study drug will be labelled with:

- name of the patient
- hospital identification number of the patient

3.6 Storage conditions

Bevacizumab should be refrigerated at 2°-8°C and should be protected from light.

Do not freeze. Fractionated in a 2.5mg/0.1mL it can be stored up to 30 days until time of use. Unused and outdated vials will be destroyed.

4. Investigational Medical Device

N/A

5. Study Protocol Summary

5.1 Study design

Longitudinal cohort study with convenience sampling.

5.2 Inclusion criteria

The study includes patients with active neovascular ingrowth and/or macular edema. The indication for treatment is set in an outpatient clinic, the intravitreal injection is administered trough day surgery setting or equivalent.

All patients must meet the following criteria for entry into the trial:

1. Age ≥ 18 years of either gender
2. Written informed consent must be obtained before any intravitreal injection of bevacizumab is performed
3. Visual impairment predominantly due to abnormal new vessel ingrowth and/or macular edema. The prescence of fluid (intraretinal, subretinal or sub-RPE) detected clinically or on the OCT.

If both eyes are eligible for the study, both eyes can be included in the study.

5.3 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in the study:

1. Women
   - Women who are pregnant or breastfeeding (pregnancy defined as the state of a female after conception until the termination of gestation, confirmed by a positive hCG laboratory test (> 5mIU/mL)
   - Women of childbearing potential must be practicing effective contraception implemented during the trial and for at least 28 days following the last dose of study medication
2. Tromboembolic event (CVA or TIA, AMI) less than 3 months prior to the intravitreal injection of bevacizumab
3. History of hypersensitivity for bevacizumab.

5.4 Primary endpoint

Evaluating the safety of intravitreal injections with bevacizumab in patients with neovascularization or macular oedema in a real-life clinical setting.

5.5 Secondary endpoints

Evaluating the efficacy of intravitreal injections with bevacizumab in patients with neovascularization or macular oedema in a real-life clinical setting.

5.6 Procedures

Clinical evaluations with dilation of the pupils. The investigator will examine the retina with the aid of a fundus lens and a slit lamp. This investigation will be performed with a 1, 3 or 6 month interval (or more frequent) as long as there are signs of disease activity. This frequency is part of the standard care for patients with abnormal vessel ingrowth and/or macular edema and will be identical to the follow-up of patients treated with licensed anti-VEGF drugs. The investigator has the right to reduce the follow-up interval.

Functional testing: ***fluoresceine angiography and ocular coherence tomography***. The necessity of these investigations is determined by the degree of activity and as deemed necessary by the investigator.

Treatment with bevacizumab is warranted if there are signs of active new vessel ingrowth and/or macular edema. It is anticipated that most (re)treatment decisions will be driven by the presence or absence of fluid (subretinal, intraretinal fluid, or sub-RPE) on the OCT. Eyes with fluid on OCT should be treated, with the exception of eyes in which there has been no decrease in fluid after three consecutive monthly injections. For such eyes, it is possible that continued treatment may be futile, and the ophthalmologist and patient may choose to suspend treatment. Treatment may be reinstituted in these eyes at a later visit if there is increased fluid (relative to the visit when treatment was stopped) on OCT.

If there is no fluid on OCT, but there are other signs of disease activity, the eye should be treated. These signs include new subretinal or intraretinal haemorrhage, persistent subretinal or intraretinal haemorrhage, decreased visual acuity relative to the last visit without another explanation, increased size of the problems on fluorescein angiography relative to the last angiogram, or leakage on fluorescein angiography.

Fluorescein angiography may be required at the discretion of the investigator to support the decision to treat.

Intravitreale injection with bevacizumab as long there is disease activity and further administration of anti-VEGF drug is required. The (re)treatment criteria in this study have evolved from the methods used by other investigators in earlier studies of intravitreal anti-VEGF agents.

Injection procedures have been adapted from the DRCR.net standard procedures and the ranibizumab guidelines (Genentech) to reduce the risk of unwanted side-effects.

Each visit, the visual acuity will be measured in the study eye and the anterior segment will be evaluated by simple slit lamp investigation. Decision to treat will be guided by dilated fundus examination and/or ocular coherence tomography, fluorescein angiography.

Recommended investigations

	BASELINE	OBSERVATION PERIOD: recommended every visit	OBSERVATION PERIOD: Annually +/- 4 months
Informed consent	x		
Visual acuity	x	x	x
Intra-ocular pressure	x		x
Slitlamp examination	x	x	x
OCT	x		x
FFA			x

The expected total duration of the study will be 30 years.

5.7 Randomisation and blinding

Not applicable, there is no randomization of blinding in the trial.

5.8 Monitoring and quality measures

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6. Study analysis

No sample size calculation or other statistical analysis were performed in this trial.

7. Independent Ethics Committee and Competent Authority

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 1, dd. 20131128* - *ICF version 1.0, dd. 20131126 (NL & FR)*	***Approval date Central EC: 22-NOV-2013***	***Approval date FAMPH: 21-MAR-2014***
Amendment 1: *>> Reason amendment: adding investigators*	***Approval date Central EC: 29-JUL-2016***	***Approval date FAMPH: 05-AUG-2016***
Amendment 2: - *Protocol version 2.0, dd. 29072016* *>> Reason amendment: updating amount of participants to 350 subjects*	***Approval date Central EC: 29-JUL-2017***	***Approval date FAMPH: 10-AUG-2016***
Progress and Safety Report 2013-2016 ****Acknowledgment of receipt***	***Submission : 16-FEB-2017*** ***AoR* : 17-FEB-2017***	***Submission FAMPH: 26-APR-2017***
Amendment 3: - *Protocol version 3.0, dd. 19072017* - *Protocol version 3.0 Summary* *>> Reason amendment: updating amount of participants to 400 subjects*	***Approval date Central EC: 31-AUG-2017***	***Approval date FAMPH: 22-SEP-2017***
Progress and Safety Report 2013-2017	***Submission and AoR EC: 05-MAR-2018***	***AoR FAMPH: 06-JUN-2018***
Amendment 5 - *Protocol version 4.0, dd. 10042018* - *Protocol version 4.0 Summary dd. 2018-04-10* *>> Reason amendment: updating amount of participants to 500 subjects*	***Approval EC: 09-MAY-2018***	***Approval FAMPH: 17-MAY-2018***

DSUR#1 (Development Safety Update Report) 2019 - *Reporting period 2018-01-01 – 2019-12-31*	***Submission EC: 2020-03-12 AoR EC: 2020-03-17***	***Submission and AoR FAMHP: 2020-03-12***
DSUR# - 2020 - *Reporting period 2020-01-01 – 2020-12-31*	***Submission EC: 2021-02-02 AoR EC: 2021-02-04***	***Submission and AoR FAMHP: 2021-02-02***
DSUR#3 - 2021 - *Reporting period 2021-01-01 – 2022-03-25*	***Submission EC: 2022-05-23 AoR EC: 2022-06-28***	***Submission and AoR FAMHP: 2022-05-23***
Notification: - *Annex to Information and Consent Form Version 1.0 dd.2013-11-26 – dd. 2022-11-18*	***Submission EC: 2022-11-18 AoR EC: 2023-07-13***	***Approval FAMHP: N.A.***
Amendment 6: - *Protocol version 5.0 dd.2022-11-21* - *Protocol version 5.0 Summary dd.2022-11-22* - *Increasing number of participants to 800*	***Approval EC: 2022-12-14***	***Approval FAMHP: 2022-12-08***
DSUR#4 - 2022 - *Reporting period 2022-03-26 – 2023-03-25*	***Submission EC: 2023-06-30*** ***AoR EC: 2023-07-03***	***Submission and AoR FAMHP: 2023-06-30***
DSUR#5 - 2023 - *Reporting period 2023-03-26 – 2024-03-25*	***Submission EC: 2024-05-07 AoR EC: 2024-05-08***	***Submission and AoR FAMHP: 2024-05-07***
End of Trial Notification	***Submission EC: 2024-07-08***	***Submission and AoR FAMHP: 2024-07-18***

8. Results

8.1 Subject enrollment and demographics

In total 583 subjects participated in the trial in the period between 25-Nov-2013 (first inclusion) until 09-Jul-2024 at the Ghent University Hospital. The last inclusion was on 20-Jun-2024 (last inclusion).

	31/12/2017	31/12/2018	31/12/2019	31/12/2020	31/12/2021	31/12/2022	31/12/2023	09/07/2024
Avastin IVT	-	-	82	91	74	71	63	81
Avastin (no IVT)	156	179	84	95	104	102	103	101
Other	5	7	10	12	15	13	19	133
FU (no treatment)	11	21	24	27	27	23	26	26
Lost to FU	56	62	78	75	69	83	80	80
Own eye doctor	17	26	31	30	32	38	40	40
Deceased	12	16	21	37	78	95	120	122
Total	**365**	**426**	**459**	**501**	**524**	**547**	**572**	**583**

Age range	**No of female subjects**	**No of male subjects**	**Total No of subjects**
23-99	287	296	583

8.2 Study specific results

Data was collected from 2013 to 2024. No other in-depth analyses were performed on the data. The safety issues were limited during the study period (see 9. Safety).

9. Safety

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, …)
103	NA	N	Sterile inflammation left eye after injection (ophthalmic SAE)	Resolved

>> Treatment; topical medication + STOP avastin + vitrectomy with internal limiting membrane peeling

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, …)
273	NA	N	Serious detachment as toxic reaction on general medication with secondary hypotony and choroidal detachment (ophthalmic SAE)	Resolved

>> Treatment: medication IV medrol + topical medication

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, …)
430	NA	N	Heart failure (cardiac SAE)	Death

>> Treatment: N/A

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, …)
445	NA	N	Malignant disorder (cardiac SAE)	Death

>> Treatment: N/A

10. Device deficiencies

Not applicable.

11. Protocol deviations

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken
2024-08-22	Minor	A signed and dated CV for Vander Eecke,Morgane could not be obtained as she has since left the hospital for the periphery, and only an unsigned/undated version is available	Note-to-File created
2024-06-12 2024-06-14 2024-06-20	Minor as content ICF has not been changed. Header altered by mistake	A non-approved version of the ICF, v2.0 dated May 2024, was obtained from subjects ID 580, 581, and 583. However, the content is identical to the approved version, v1.0 dated 2013-11-26. The only difference is that the version information was placed in the header of the non-approved version, whereas in the approved version, it is mentioned in the footer.	Note-to-File created + reminder for future ICF's
2024-07-12 2024-08-05	Major as this issue occurred also during MV#5 and reminder not followed-up	The delegation for Sambaer Julie and Dr. Ruys Joke was not countersigned by the PI in a timely manner on the Site Delegation Log.	Reminded for future studies
2024-07-12 2024-08-05	Major as this issue occurred also during MV#5 and reminder not followed-up	The registration for Sambaer Julie and Dr. Ruys Joke on the Site Delegation Log were only completed on 2024-07-12 and 2024-08-05, indicating a significant delay in updating the logs as this has been requested on 2024-05-29	Reminded for future studies

Subject number	Date of deviation (yyyy-mm-dd)	Category*	Classification** Minor/ Major/Critical	Description of deviation	Action taken	Name/signature site staff
550	2023-02-17	IMP	Minor N.A	Lot number and expiry date not documented in Eyefile for the injection performed on 17/02/2023 Qp incorrect.	Retraining during MV#5	
555	2023-07-05	Safety	Minor	AE suspicion TIA not reported	Retraining during MV#5	See below cel LdL 23-05-2024
562	2023-11-03	ICF	Minor	Subject did not sign ICF. Considered as minor as subject provided name and date.	Retraining during MV#5	

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken	Name/signature site staff
2024-03-04 2024-05-13	Major	**Site Delegation log not completed:** Dr. Ruys Joke obtained consent on 2024-03-04 and 2024-05-13. She was not delegated to perform this task	Retraining during MV#5	See signature of the PI on page 2
2023-09-15, 2024-02-06 2024-03-22	Major	**Site Delegation log not countersigned by the PI in a timely manner:** Countersignature was not registered by the PI in a timely manner (1 to 3 months after performing study related tasks) for 4 Investigators (Baetens Matthieu, Mourisse Sofie, Hoebeke Lana, Bourdeaud'huy Liesl)	Retraining during MV#5	See signature of the PI on page 2
2024-03-04 2024-05-13	Major	**Site Training log not completed:** Study team member Dr. Ruys Joke performed tasks without registration on the training log (Obtaining ICF)	Retraining during MV#5	See signature of the PI on page 2
Between 2023-08-30 and 2024-03-22	Major as this issue occurred also during MV#4 and reminder not followed-up	**No GCP certificate available** for 2 investigators (Vander Eecke Morgane and Ruys Joke) during the trial and therefore it could not be proven that the study team is adequately qualified to perform their trial-related tasks (No ICF has been obtained, only SOC injection with Avastin[9])	Retraining during MV#5	See signature of the PI on page 2
2023-09-13 2024-03-04	Major as this issue occurred also during MV#4 and reminder not followed-up	**No signed and dated CV available** for 7 investigators (Mourisse Sofie, Vander Eecke Morgane ,Hoebeke Lana Bonny Paulien, Bourdeaud'huy Liesl, Alluyn Lien and Ruys Joke) and therefore it could not be proven that the study team is adequately qualified to perform their trial-related tasks	Retraining during MV#5	See signature of the PI on page 2

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken	Name/signature site staff
2023-01-19	Minor	**Site Delegation log not correctly completed:** Prof. Dr. Leroy Bart did not provide his full name, responsibility and initials himself. Date of completion is not the actual date of completion but a date in the past (2023-06-03 instead of 2023-01-19.	Retraining during MV#4	Henderick Hilde
2023-01-20	Minor	**Site Delegation log not correctly completed:** Dr. Vermorgen Koen did not provide his full name, responsibility and initials himself	Correction of the date of completion by the SC and retraining during MV#4	Henderick Hilde
2022-12-21	Minor	**Site Training log not correctly completed:** Study team member Dr. Deschuttere Charles performed tasks without registration on the training log (SOC injection with Avastin®)	Retraining during MV#4	Deschuttere Charle
2022-11-17	Minor	**No GCP certificate available** for 3 investigators during the trial and therefore it could not be proven that the study team is adequately qualified to perform their trial-related tasks (No ICF has been obtained, only SOC injection with Avastin®)	Retraining during MV#4	DE ZAEYTIJD JULIE
2022-12-21	Minor	**No signed and dated CV available** for an investigator (Deschuttere Charles) and therefore it could not be proven that the study team is adequately qualified to perform their trial-related tasks	Retraining during MV#4	Deschuttere Charle

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken	Name/signature site staff
2023-01-20	Minor	**No signed and dated CV available** for an investigator (Van Den Bosch Carole) and therefore it could not be proven that the study team is adequately qualified to perform their trial-related tasks	Retraining during MV#4	Van Den Bosch Carole

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken	Name/signature Sponsor (representative)
2023-05-24	Minor	DSUR not submitted within 60 calendar days from the DSUR data lock point (DLP), which was 2023-05-24, despite receiving reminders from HIRUZ on 2023-03-29, 2023-05-08 and 2023-05-16, regarding adherence to the reporting timeline requirements. The report was only finalized by the Principal Investigator (PI) during the MV on 2023-06-29.	Report finalized during the MV#4 dd. 2023-06-29 and CI/PI trained. DSUR submitted to the competent authorities on 2023-06-30.	DE ZAEYTIJD JULIE

**Critical Deviation (Serious Breach):* *A deviation that has a major impact on the safety and/or rights of subjects or the quality of their data is regarded as a critical deviation.*

**Major Deviation:* *A deviation that might have a major impact on the safety and/or rights of subjects or the quality of their data is regarded as a major deviation.*

**Minor Deviation:* *A deviation that does not have a major impact on the safety and/or rights of subjects or the quality of their data is regarded as a minor deviation*

Subject number	Date of deviation (yyyy-mm-dd)	Category*	Classification** Minor/ Major/Critical	Description of deviation	Action taken	Name/signature site staff
548	2023-12-01	ICF not completed correctly	Minor	The ICF was not completed correctly by the subject. An incorrect date has been registered	Retraining during MV#4	DE ZAEYTIJD JULIE

**(1) ICF (2) Eligibility (3) Study-specific Interventions (4) IMP/IMD (5) Concomitant Medication (6) Safety Reporting (7) Discontinuation (8) Other*

***Critical Deviation (Serious Breach):* *A deviation that has a major impact on the safety and/or rights of subjects or the quality of their data is regarded as a critical deviation.*

***Major Deviation:* *A deviation that might have a major impact on the safety and/or rights of subjects or the quality of their data is regarded as a major deviation.*

***Minor Deviation:* *A deviation that does not have a major impact on the safety and/or rights of subjects or the quality of their data is regarded as a minor deviation*

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken
2020-12-17	Critical	Site enrolled more that the allowed 500 participants in the trial, without submitting an amendment. Site misunderstood that the total recruited subjects are all subjects who received at least one time IMP and thus also include subjects who are lost to FU, decided to go to their own ophthalmologist and who deceased.	HIRUZ to report this critical finding to the ethics committee. Submission of amendment N°6 asap. However, due to the medical need and urgency, anyone who is not eligible for the reimbursement conditions for the Lucentis® and Eylea® will be included in the trial even though the number to be recruited has been exceeded Retraining during MV#3 dd.2022-11-17 & 18 .
2020-12-17	Minor	The reported SAE's for subject ID 39 and 63 should not have been reported	Retraining during MV#3 dd.2022-11-17 & 18
2020-04-02	Minor	The reported SAE for subject ID 430 should not have been reported	Retraining during MV#3 dd.2022-11-17 & 18
2019-05-26	Major	SAE of subject ID 273 is not reported within 48 hours after becoming aware of the event	Retraining during MV#3 dd.2022-11-17 & 18

Date of deviation (yyyy-mm-dd)	Classification *Minor/ Major/Critical	Description of deviation	Action taken
2017-06-07	Minor	Follow up of SAE of subject ID 103 is not reported to HIRUZ	Retraining during MV#3 dd.2022-11-17 & 18
2017-06-03	Minor	Prof. dr. Leroy Bart who obtained consent is not listed on the delegation log.	Retraining during MV#3 dd.2022-11-17 & 18
2017-09-22	Minor	Dr. Vermorgen Koen who obtained consent is not listed on the delegation log.	Retraining during MV#3 dd.2022-11-17 & 18
2019-5-03	Minor	Dr. Balikova Irina who obtained consent is not listed on the delegation log	Retraining during MV#3 dd.2022-11-17 & 18
2018-07-19	Major	Subject signed ICF after first assessment is done. Investigator signed ICF on 2018-07-19 and the subject on 2018-07-20. First IMP administered on 2018-07-19.	Retraining during MV#3 dd.2022-11-17 & 18
Before first quarter of 2016	Potentially major	No drug accountability documented	None as lot numbers and expiry dates cannot retrieved anymore
Since trial start	Minor	IMP not labelled although this is described in the protocol	None. No labeling will occur as this is a pragmatic trial

12. Discussion and overall conclusions

In recent times, with the advent and increasing use of anti-VEGF agents for the intraocular use, there has been a paradigm shift in the management of various medical retinal pathologies including neovascular AMD, diabetic retinopathy, DME, and RVO. Numerous trials conducted worldwide (CATT trial, IVAN trial, GEFAL, MANTA) on thousands of patients have shown intravitreal bevacizumab (Avastin) to be noninferior to ranibizumab (Lucentis) in terms of efficacy and safety. Bevacizumab also has the advantage of reducing the cost of therapy, especially in developing countries where the population's access to resources is limited, and it helps to reduce the financial burden of multiple injections.

Although intravitreal bevacizumab (Avastin) continues to be an off-label therapy used in the treatment of ocular disorders, it remains to be the preferred agent of retinal physicians worldwide. For chronic diseases such as DME and AMD, that require frequent dosing, bevacizumab provides an ideal economical choice of treatment, especially in the developing nations. However, aliquoting of bevacizumab and its potential ocular and systemic adverse reactions continue to remain the limiting factor for its extensive use.

Safety was prioritised as the primary endpoint in this trial. It can be concluded that intravitreal bevacizumab is safe to use. Because no data analysis was performed, no conclusion can be made for the secondary endpoint (efficacy).

13. References

- Ranibizumab and bevacizumab for neovascular age-related macular degeneration.

CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ.

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Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, Reeves BC; IVAN study investigators.

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- Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial.

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