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Official Title:	An open-label, multicenter rollover study to provide continued treatment with anetumab ravtansine for participants with solid tumors who were enrolled in previous Bayer-sponsored studies
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Title Page

Protocol Title:

An open-label, multicenter rollover study to provide continued treatment with anetumab ravtansine for participants with solid tumors who were enrolled in previous Bayer-sponsored studies

Protocol Number: 20322
Amendment Number: 2

Compound Number: BAY 94-9343

Study Phase: Phase 2

Short Title: Anetumab ravtansine rollover study

Sponsor Name and Legal Registered Address:

Sponsor (Non-US):

Bayer AG, D-51368 Leverkusen, Germany

Sponsor (US territory):

Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, New Jersey 07981-0915, USA

Regulatory Agency Identifier Number(s)

IND: 109169

EudraCT: 2019-000061-20

Approval Date: 18 JUN 2019

Sponsor Signatory

PPD

PPD

PPD

Date

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	18 JUN 2019
Amendment 1	10 JAN 2019
Original Protocol	07 DEC 2018

Amendment 2 (18 JUN 2019)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Technical correction of hidden text format in figure and tables footnote styles.

Section # and Name	Description of Change	Brief Rationale
Figure 1-1: Study schema Table 1-1: Schedule of activities Table 6-1: Bayer classification and management of corneal epitheliopathy Table 6-2: Bayer classification of visual acuity changes	Footnotes previously not visible due to technical error were made visible.	Technical correction to ensure all footnotes are visible.
Sponsor Signatory	Due to role title change, the Sponsor Signatory's title was updated from Global Clinical Leader (GCL) to Sr. Clinical Development Leader (CDL).	Administrative change.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: An open-label, multicenter rollover study to provide continued treatment with anetumab ravtansine for participants with solid tumors who were enrolled in previous Bayer-sponsored studies

Short Title: Anetumab ravtansine rollover study

Rationale: The purpose of this study is to collect long-term safety information on anetumab ravtansine and to enable patients who received an anetumab ravtansine-containing treatment in any Bayer-sponsored anetumab ravtansine parent study, to continue to receive study treatment and/or, if applicable, follow-up at the time of parent study closure.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• Safety	• Incidence of TEAEs • Incidence of TESAEs • Incidence of Drug-related TEAEs and TESAEs
Secondary	
• Survival	• Overall survival (OS)
Tertiary/Exploratory	
• Tumor response	• Investigator determined tumor assessment

Overall Design:

Disclosure Statement:

This is an open-label rollover study to enable participants having received anetumab ravtansine in any applicable Bayer sponsored anetumab ravtansine parent study, to continue treatment or follow up (as per current epoch of parent study) at the time of parent study closure.

Number of Participants:

Participants who are currently receiving treatment or follow-up in ongoing anetumab ravtansine studies may be eligible to enroll in the study. There may be periods when there are no active participants in this study but it will remain open for enrollment.

Intervention Groups and Duration:

The start of the treatment period is defined by the first administration of study medication in the rollover study. Participants will be treated in 21-day cycles with Q3W IV administration of anetumab ravtansine. Participants will continue treatment with study treatment until any of the discontinuation criteria specified in Section 7.2 occur.

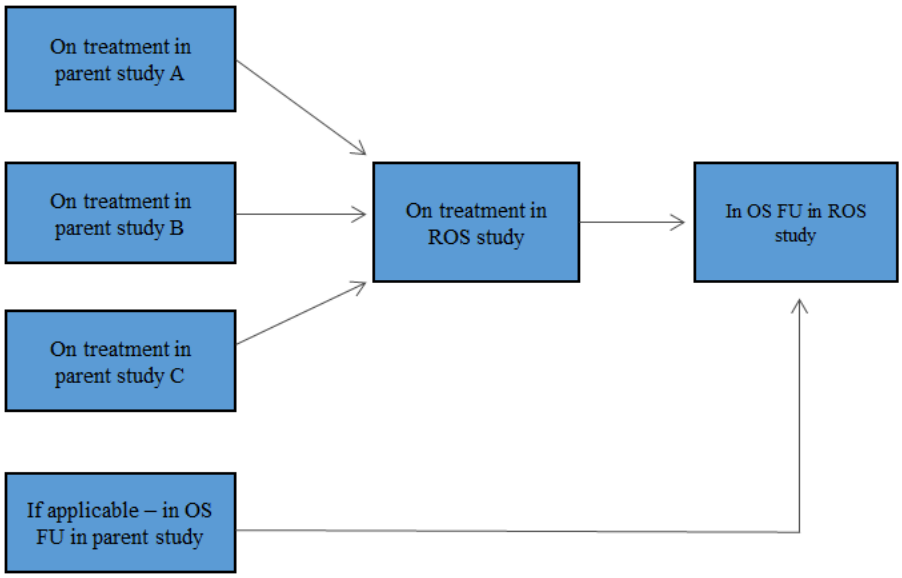
After permanent discontinuation from study medication, a safety follow up visit will take place 30-35 days after the last dose of study medication was administered and participants may enter long-term follow up for OS.

Data Monitoring Committee: No

1.2 Schema

The design of the study is represented in Figure 1–1.

Figure 1–1: Study schema



Abbreviations: FU = Follow-up; OS = Overall survival; ROS = Rollover study

1.3 Schedule of Activities (SoA)

Table 1–1: Schedule of activities

Procedure	Screening[a,b]	Cycle X Day 1 (on treatment)	Safety FU (30-35 days after last dose)	Long term FU (every 3 months)	Notes
Informed consent	X				For applicable parent studies, effort should be made to obtain informed consent to continue to collect survival information in study 20322 for participants in active and/or long-term FU.
Inclusion and exclusion criteria	X	X			Information to assess if participant can receive 1st administration of study treatment, which is obtained within maximum 7 days prior to ICF for ROS signature can be used. Only to be reviewed on C1D1.
Serum pregnancy test	X	X	X		For women of childbearing potential, performed maximum 7 days prior to study intervention administration. For screening, on-study pregnancy test methods of parent protocols are acceptable.
Demography/Diagnosis	X				
Cancer Classification	X				

Procedure	Screening[a,b]	Cycle X Day 1 (on treatment)	Safety FU (30-35 days after last dose)	Long term FU (every 3 months)	Notes
Medical history	X				For on-treatment participants: Prior clinical and surgical conditions and relevant events that occurred during the course of parent study. Relevant events are defined as (S)AE's leading to dose reduction or dose interruption/delay
Study drug administration		X			Study drug (s) dosing and treatment schedule as per parent study protocol.
Vital signs	X	X			A 1-day window pre-administration is allowed.
Brief physical examination	X	X			A 1-day window pre-administration is allowed.
Complete blood count and differential	X	X	X		A 3-day window pre-administration is allowed.
AST/ALT/total bilirubin/creatinine	X	X	X		A 3-day window pre-administration is allowed.
Ophthalmological examination	X	X	X		Every other cycle during treatment, and at the discretion of the investigator in consultation with the ophthalmologist. Can be performed up to 7 days before the planned drug administration. Examinations to be performed per the instructions of the parent study. For screening, testing time schedule of parent study will be accepted – results >7 days would be acceptable provided no ocular symptoms have arisen since the latest test.

Procedure	Screening[a,b]	Cycle X Day 1 (on treatment)	Safety FU (30-35 days after last dose)	Long term FU (every 3 months)	Notes
AE/SAE review	X	X	X		Any (S)AE in the parent study which is ongoing at the time of signing informed consent for the rollover study, must be reported as (S)AE in the rollover study and re-graded to CTCAE V5.0. Further follow-up and documentation should occur in the rollover study.
Concomitant medication review	X	X	X		For on-treatment participants: documentation of concomitant medication ongoing at the time of parent study closure, and any new concomitant medication started after signing of ICF
Survival status and new or ongoing anti-cancer treatment				X	
Collect local tumor response information		X			Collect local imaging information (assessment date and outcome) obtained as per standard of care
IxRS	X	X	X		Inform IxRS of end of Treatment in ROS as soon as possible, at the latest at Safety FU visit

Abbreviations: AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; C1D1 = Cycle 1 Day 1; FU = Follow-up; ICF = Informed consent form; IxRS = Interactive voice/web response system; ROS = Rollover study; SAE = Serious adverse event

a. The treating investigator should ensure a seamless transition without a change in the treatment schedule. Any treatment interruption for medical reasons between last administration in the parent study and first administration in this study should not exceed 42 consecutive days.
b. During the last planned visit in the parent study, ROS eligibility criteria will be reviewed and the participants may sign informed consent for the rollover study. After signature of ROS ICF, any further procedures/events including C1D1 drug administration are part of the ROS and will be documented there.

2. Introduction

There are currently multiple ongoing anetumab ravtansine clinical studies and some of the participants in these studies will still be ongoing at the time when their clinical study is planned to be closed. The intention of this rollover study is to enable participants, who are still benefiting from treatment, to continue to receive treatment in the rollover clinical study instead of parent study. For applicable studies, patients in active and/or long-term follow up will also be enrolled in this rollover study for continued follow up.

2.1 Study Rationale

The purpose of this study is to collect long-term safety information on anetumab ravtansine and to enable patients who received an anetumab ravtansine-containing treatment in any Bayer-sponsored anetumab ravtansine parent study, to continue to receive study treatment and/or, if applicable, follow-up at the time of parent study closure.

2.2 Background

Since a variety of malignancies show high expression of mesothelin (1), several agents are in development to target cell surface mesothelin expression. Among these novel agents are the ADCs, which combine the specific targeting of an antibody with the potency of cytotoxins (2).

Anetumab ravtansine (BAY 94-9343) is an antibody-drug conjugate (ADC) consisting of a fully human immunoglobulin G1 (IgG1) antibody (BAY 86-1903) directed at mesothelin antigen and conjugated to a synthetic cytotoxic anticancer agent, maytansine derivative (DM4, BAY 1006640) as toxophore through a reducible disulfide linker.

Anti-tumor activity of anetumab ravtansine as a single agent or in combination with standard of care agents *in vivo* has been demonstrated in human tumor models exogenously and endogenously expressing mesothelin as well as in patient-derived xenograft tumor models. For more information, see the most recent investigator's brochure (IB) for BAY 94-9343 anetumab ravtansine.

2.3 Benefit/Risk Assessment

Only participants, who have been receiving treatment in any applicable previous Bayer-sponsored anetumab ravtansine parent study, will be enrolled in this study. The on-treatment participants will continue anetumab ravtansine monotherapy or combination therapy at the dose level(s) that have been established and were well-tolerated by the respective participant in the parent study before. The study investigator of the anetumab ravtansine study, to which the participant is initially assigned, is expected to assess the overall benefit/risk for each participant. If the investigator deems there is a positive benefit/risk assessment, the participant can continue to receive treatment in this rollover study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of anetumab ravtansine may be found in the Investigator's Brochure. For combination treatment drugs, please refer to their respective prescribing information.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Safety	• Incidence of TEAEs • Incidence of TESAEs • Incidence of Drug-related TEAEs and TESAEs
Secondary	
• Survival	• Overall survival (OS)
Tertiary/Exploratory	
• Tumor response	• Investigator determined tumor assessment

4. Study Design

This is an open-label rollover study to enable participants having received anetumab ravtansine in any applicable Bayer sponsored anetumab ravtansine parent study, to continue treatment or follow up (as per current epoch of parent study) at the time of parent study closure.

4.1 Overall Design

The on-treatment participants in this open-label study will continue receiving the prior study therapy at the dose level previously assigned and well tolerated, under the following conditions:

- the participant is continuing to derive clinical benefit from the treatment as assessed by study investigator
- until participant withdraws consent
- until participant is non-compliant to the protocol requirements
- until participant is lost to follow-up
- until an unacceptable toxicity or death occurs

During the last planned visit of the parent study, if the eligibility criteria for the rollover study are met, the participants may sign informed consent for the rollover study. After signature of ROS ICF, any further procedures/events including C1D1 drug administration are part of the ROS and will be documented in the ROS eCRF.

The treating investigator should ensure a seamless transition without change in the treatment schedule. Any medically-indicated treatment interruption between last administration in the parent study and first administration in this study should not exceed 42 consecutive days.

For participants in active or long term follow-up in the applicable parent studies, efforts should be made to obtain signed informed consent for the rollover study. When the signature is obtained, the survival follow-up and evaluation of safety can continue in the rollover study for up to 5 years.

Details of medical history must be recorded in the participant's source documents and entered in the eCRF as required.

The study investigator will continually assess the clinical benefit/risk of anetumab ravtansine treatment when the participants visit the clinical site for their continued treatment and will ensure that participants who meet any of the withdrawal criteria above discontinue treatment.

Safety assessments should be performed according to the protocol, either at the study site or by the participants' healthcare professional. Additional safety assessments may be performed at investigator's discretion.

During screening, the following information will be recorded in the rollover study eCRF:

- Demography including study number and participant's identification number of the parent study
- Medical history
- Inclusion/exclusion criteria
- Ongoing (S)AE's (re-graded per CTCAE V5.0)
- Any new (S)AE's
- Concomitant medications

4.2 Scientific Rationale for Study Design

Not applicable for this rollover study.

4.3 Justification for Dose

Not applicable for this rollover study.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled activity shown in the Schedule of Activities.

The end of the study is defined as the date when the last participant has completed the study and the sponsor has decided to close the trial.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants ongoing in an applicable Bayer-sponsored anetumab ravtansine parent study at the time of its planned study closure.
- For on-treatment participants: participant is eligible to receive the next dose of study intervention per the parent study protocol.

- For on-treatment participants: any ongoing adverse events that require temporary treatment interruption must be resolved to baseline grade or assessed as stable and not requiring further treatment interruption. For applicable studies: should treatment be permanently interrupted in the parent study, participants may be enrolled in the follow-up portion of the rollover study.
- Women of childbearing potential and men with reproductive potential must be willing to continue practicing acceptable methods of birth control during the study treatment and until 6 months after stopping study treatment. Genetic consultation is recommended if the participant wishes to have children after ending treatment. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. The investigator or a designated associate is requested to advise the participant how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods include:
    - Combined (estrogen and progesterone containing: oral, intravaginal, transdermal) and progesterone-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.
    - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
    - Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
    - Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant).

  Male participants with a female partner of childbearing potential must use a condom and ensure that an additional form of contraception is also used during treatment and until 6 months after last study drug administration.
- Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. For on-treatment participants: a positive serum pregnancy test.

Prior/Concomitant Therapy

2. For on-treatment participants: use of one or more of the prohibited medications listed in the respective parent study protocol.

Other Exclusions

3. Participant is unable to comply with the requirements of the study as described in the SoA.
4. Participants who are receiving SOC agent(s) but not anetumab ravtansine in the parent study, and are able to receive SOC agent outside of the clinical study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

For prohibited food and drink items, please refer to parent study protocols sections on prohibited concomitant therapies.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

In case there would be a medically-indicated treatment interruption between last drug administration in the parent study and first drug administration in this study of more than 42 consecutive days, the participant will also be considered to be a screen failure.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The following investigational products will be used in the study:

- Anetumab ravtansine
- Any other medication as specified in the parent study protocol used in combination with anetumab ravtansine.

Participants will be treated with the anetumab ravtansine/study medication as per the dosing instructions from the parent study protocol in a Q3W schedule.

	Anetumab ravtansine	Combination drug
Intervention Name	BAY 94-9343 / Anetumab ravtansine	Medication as specified in the parent study protocol used in combination with anetumab ravtansine
Type	Drug; experimental	Drug
Dose Formulation	Lyophilizate	As specified in the parent study protocol
Unit Dose Strength(s)	Each vial contains 62.5 mg of anetumab ravtansine; the amount	As specified in the parent study protocol

	Anetumab ravtansine	Combination drug
	available for administration, based on retractable volume of reconstituted solution is 60 mg of anetumab ravtansine	
Dosage Level(s)	As per the dosing instructions from the parent study protocol in a Q3W schedule	As per the dosing instructions from the parent study protocol
Route of Administration	IV infusion	As specified in the parent study protocol
IMP and NIMP	IMP	As specified in the parent study protocol
Sourcing	Provided by the Sponsor	Will be at the discretion of the sponsor and can potentially change from central to local supply by the sponsor, to supply per prescription or any other available option.
Packaging and Labeling	Provided in 30 mL injection vials. Each vial will be labeled as required per country requirement.	As specified in the parent study protocol
Current/Former Name(s) or Alias(es)	Not applicable	As specified in the parent study protocol

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the handling, preparation, administration of study interventions, and the final disposition of unused study interventions are provided in the Storage and Handling Instructions and the respective prescribing information

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open label study and there will not be any randomization or blinding.

Attempts will be made to enroll all eligible participants from the applicable parent studies.

6.4 Study Intervention Compliance

The administration of all study treatments will follow the schedule of their respective parent study. Each administration must be recorded in the source documentation and on the CRF.

Reasons for dose interruption / delay, reduction, re-escalation or omission will also be recorded in the source documents and on the CRF.

An adequate record of receipt, distribution, and return/destruction of all study treatment must be kept in the form of a Drug Accountability Form.

The preparation and administration of all study treatment will be performed by members of the investigator team during hospitalization and site visits. These persons will ascertain and document that the participant receives all treatments as planned.

6.5 Concomitant Therapy

For concomitant therapy in this ROS, the requirements of the respective parent study protocol should be followed. For more details on permitted and prohibited concomitant medication during study, refer to parent study protocol.

Participants should be closely monitored for side effects of all concomitant medications regardless of path of elimination.

All ongoing concomitant medications (including start/stop dates, total daily dose, and indication) must be recorded in the participant's source documentation and in the eCRF. Concomitant use of contrast media need not be recorded unless the participant experiences an AE and there is a reasonable possibility that the event might have been caused by exposure to contrast media.

Please refer also to the latest version of the Investigator's Brochures for anetumab ravtansine and prescribing information of combination treatments for guidance when prescribing other medications.

6.6 Dose Modification

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 will be used to assess toxicities; in addition, a Bayer grading system (see Table 6–1 and Table 6–2) will be used to assess corneal epitheliopathy and visual acuity changes.

Treatment-emergent (serious) adverse event (TE(S)AE) requiring dose modification (dose omission, infusion interruption, change in infusion rate, dose delay, dose reduction, or permanent discontinuation of study intervention[s]) will be defined as an adverse event that is possibly, probably, or definitely related to study intervention(s) and occur any time during the study.

For dose modification of the study intervention(s) following TE(S)AE's, please refer back to the relevant parent protocol guidelines. These remain valid also under CTCAE V5.0 AE assessment.

Table 6–1: Bayer classification and management of corneal epitheliopathy

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Corneal morphology	No pathologic changes	Any stage of superficial punctate keratitis [a]	Epithelial opacities Micro-cysts Micro-deposits Corneal erosion Stromal opacity: non-central	Corneal ulcer without risk of acute rupture Stromal opacity: central	Corneal ulcer more severe than Grade 3
Eye treatment [b]	Ocular lubricants at the discretion of investigator in consultation with ophthalmologist	Ocular lubricants; add topical steroids if superficial punctate keratitis shows treatment-emergent progression by ≥ 2 SPK Grades	Intensive treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator in consultation with ophthalmologist	Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recommended at the discretion of investigator in consultation with ophthalmologist	Intensive therapy with lubricants, ointments, topical steroids and antibiotics as needed; occlusion or therapeutic contact lens recommended; amniotic membrane transplant and other locally approved therapies to be considered at the discretion of investigator in consultation with ophthalmologist
Anetumab ravtansine [c]	No change	No change	Keep treatment dose level and schedule if the ophthalmological exam can be performed as needed; otherwise consider dose reduction by -1 dose level without dose schedule change at the discretion of investigator in consultation with ophthalmologist [d]	1) Decrease dose to -1 dose level (or -2 dose level if event does not resolve to Grade ≤ 2 at the -1 dose level within 21 days) [d] 2) Re-start at the original dose level if the first Grade 3 event resolves to Grade ≤ 2 within 21 days and does not recur [d] 3) If not resolved within 21 days continue at reduced -1 dose level (or -2 dose level) [d]	Discontinue treatment

MTD = Maximum tolerated dose; SPK = Superficial punctate keratitis

a Oxford Schema must be used for grading SPK from stage 0 to V (see Appendix 10.6).

b Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.

c Treatment decisions are based on corneal epitheliopathy only, not on visual acuity changes

d If the MTD of anetumab ravtansine is set at 5.5 mg/kg for either cholangiocarcinoma and/or pancreatic adenocarcinoma, only one dose reduction to 4.5 mg/kg will be allowed. If the MTD of anetumab ravtansine is set at 4.5 mg/kg for either cholangiocarcinoma and/or pancreatic adenocarcinoma, no dose reductions will be allowed; toxicities requiring dose reductions in this instance will result in permanent discontinuation of anetumab ravtansine.

Table 6–2: Bayer classification of visual acuity changes

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Visual acuity	No findings, no reporting from the patient	Symptomatic visual acuity loss < 3 lines (ETDRS equivalent [a])	Visual acuity loss ≥ 3 lines, but < 6 lines (ETDRS equivalent [a])	Visual acuity loss ≥ 6 lines (ETDRS equivalent [a]	Visual acuity loss ≥ 6 lines (ETDRS equivalent [a]) leading to blindness

ETDRS = Early Treatment Diabetic Retinopathy Study

a In the ETDRS chart, each loss of 3 lines corresponds to halving the visual acuity. In other charts, an equivalent amount of visual acuity loss must be reached in order to meet this threshold.

6.7 Intervention after the End of the Study

There is no planned intervention following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

All participants who enter the study should complete all applicable study periods. Participants can be withdrawn from any study period at any time. Withdrawal from the intervention period alone does not constitute withdrawal from the study.

Participants who withdraw from the intervention period for any reason are to be encouraged to remain on the study for follow-up. Participants are expected to participate in follow-up unless they explicitly object. Withdrawal of consent to the intervention period should be documented in the participant's medical record. If the participant does not wish to be followed up further, this additional consent withdrawal for follow-up must also be documented.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for OS and new anti-cancer treatment. See the SoA for data to be collected at the time of discontinuation of study intervention.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Section 6.6 or if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Study intervention may need to be discontinued for other reasons as specified in the parent study protocols – refer to respective parent study protocol for full set of discontinuation rules.

7.1.1 Temporary Discontinuation

For temporary interruption of study intervention please refer to Section 6.6. The duration of study intervention interruption for medical reasons should not exceed 42 days.

7.1.2 Rechallenge

Rechallenge should be done according to criteria specified in Section 6.6. The duration of study intervention interruption for medical reasons should not exceed 42 days.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant must be withdrawn from the study at any time at his/her own request.
- A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, and additionally requests destruction of her/his samples taken but not yet tested, the investigator must document this (either destruction by site or request to central lab, as applicable) in the site study records.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

There will be no formal assessment of tumor response during the rollover study. Outcome of local tumor evaluation per local standard of care will be documented by the site.

Data on survival will be collected by the site.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality.

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, weight and blood pressure will be assessed.

- Blood pressure has to be measured in a consistent manner throughout the study.
- Body weight to be assessed without shoes.

8.2.3 Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.4 Ophthalmological examinations

Ophthalmological examinations to be performed as per the parent study. However, the frequency and timing of the examinations should be as per this rollover study protocol.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs, considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention (see Section 7). Events of Special Interest have to be followed up regardless of causality or relationship to study intervention.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All (S)AEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).

For on-treatment participants, the following must be documented in the medical history section of the eCRF: prior clinical and surgical conditions and also relevant events that occurred during the course of parent study. Relevant events are defined as AE's leading to dose reduction, interruption/delay.

Any AE/SAE in the parent study which is ongoing at the time of signing informed consent for the rollover study must be reported in a new CRF page on the rollover study, per CTCAE V5.0, or Bayer Grading system for corneal epitheliopathy events. Further follow-up of these events will occur in the rollover study.

Medical occurrences that begin before the start of study intervention in this study but after obtaining informed consent will be recorded on the AE section of the case report form (CRF).

Medical occurrences that started before but deteriorated after obtaining informed consent will be recorded as adverse events.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after the safety follow-up visit. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be

reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 10.3.5), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 6 months past the last administration of study drug.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4 Treatment of Overdose

In this study, any dose of anetumab ravtansine greater than 6.5 mg/kg, with an absolute maximum of 650 mg for a participant weighing 100 kg or more within a 21 day period, will be considered an overdose. For participants with dose reduction to 5.5 mg/kg or 4.5 mg/kg or 3.5 mg/kg, corresponding absolute maximum dose will be 550 mg, 450 mg and 350 mg respectively for a participant weighing 100 kg or more.

The sponsor does not recommend specific treatment for an overdose.

There is no specific antidote for anetumab ravtansine overdose. Overdosage following the administration of anetumab ravtansine should be treated as clinically indicated with symptomatic support.

In the event of an overdose, the treating physician should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
2. Obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
3. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF).
4. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

For detailed guidance on overdosing please refer to the most current version of the IB.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

9. Statistical Considerations

Data from participants who are transferred to a rollover study may be pooled and analyzed together with the data from the study in which the participant was initially included.

Data will be presented in data listings or analyzed using summary or frequency statistics. Time-to-event variables may be analyzed using Kaplan-Meier or other descriptive methods.

9.1 Statistical Hypotheses

No confirmatory statistical hypothesis testing is planned. All safety/efficacy analyses will be done in a descriptive manner.

9.2 Sample Size Determination

No formal sample size estimation will be done.

Participants of on-going or future parent studies will be enrolled in the study; therefore the number of participants is not predictable.

9.3 Populations for Analyses

For purposes of statistical analysis, the following analysis sets are defined:

Analysis set	**Description**
Enrolled	All participants who signed the ICF
Safety	All participants who take at least 1 dose of study intervention within this rollover study.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Any endpoint not designated as primary or secondary is considered to be exploratory.

9.4.1 Efficacy Analyses

The secondary endpoint overall survival will be analyzed for applicable participants using Kaplan-Meier or other descriptive methods as specified in the SAP. Data from subjects in this rollover study may be combined with data from the parent study to explore long-term survival.

Investigator-determined tumor response will be collected as an exploratory endpoint and presented in data listings. Other descriptive analyses may be detailed in the SAP.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Population.

The incidence of TEAEs, treatment-emergent serious adverse events (TESAEs), and drug-related TEAEs and TESAEs are primary endpoints and will be summarized overall and by

MedDRA term and maximum CTCAE grade or Bayer Severity Grading system. Additional presentations of corneal toxicity and other types of adverse events may be described in the SAP.

Laboratory assessments, vital signs, and ophthalmologic examinations will be presented in data listings. Summary statistics may be presented, as specified in the SAP. The incidence of lab toxicities may be summarized in frequency tables.

9.5 Interim Analyses

No formal interim analysis is planned.

10. Supporting Documentation and Operational Considerations

The focus of this rollover study is to provide anetumab ravtansine to participants and to collect safety and efficacy information as specified in the SoA.

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development phases 2, 3 and 4 and phase 1 trials in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9 Publication Policy

Not applicable. It is not planned to publish data from this study, it might be that rollover study data will contribute to publications on parent study data.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in
- Table 10–1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Serum Pregnancy Testing

Table 10–1: Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet count</td><td colspan="2" rowspan="4">White blood cell (WBC) count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>Red blood cell (RBC) count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Aspartate Aminotransferase
(AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total bilirubin</td></tr>
<tr><td colspan="2">Creatinine</td><td>Alanine Aminotransferase
(ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Highly sensitive Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)

The results of each test must be entered into the case report form (CRF).</td></tr>
</table>

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Bayer's pharmacovigilance department in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Bayer's pharmacovigilance department. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Bayer's pharmacovigilance department.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it as per CTCAE V5.0. For corneal epitheliopathy events and visual acuity changes, Bayer grades should be applied as per Table 6–1 and Table 6–2.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence,

Assessment of Causality

and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Bayer's pharmacovigilance department. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Bayer's pharmacovigilance department.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Bayer's pharmacovigilance department to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Bayer's pharmacovigilance department within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer's pharmacovigilance department via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Bayer's pharmacovigilance department will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data

SAE Reporting to Bayer's pharmacovigilance department via an Electronic Data Collection Tool
collection tool in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form. • Contacts for paper SAE reporting can be found in the SAE paper template.

10.3.5 Adverse events of special interest

Anetumab ravtansine is an investigational drug and current knowledge of the AEs associated with this compound is limited.

As with any new chemical entity, there is always potential for unexpected AEs, including hypersensitivity reactions.

Corneal epitheliopathy is considered as AE of special interest. Specific dose modification schemes are defined in the parent study protocols. An alternative severity grading system for corneal epitheliopathy will be used in addition to the CTCAE criteria, since the CTCAE may not adequately capture the severity of these novel adverse reactions, also specific dose modifications are in place (see Table 6–1 and Table 6–2). The relationship to treatment and the intensity of corneal epitheliopathy will be determined by the investigator, in consultation with the ophthalmologist.

Infusion-related reactions (IRR) are considered as AE of special interest. These adverse drug reactions are often associated with the administration of monoclonal antibodies and other therapeutic agents. Generally they are defined as 'any signs or symptoms experienced by patients during the infusion of pharmacologic or biologic agents or any event occurring on the first day of drug administration' (3). All adverse events that are diagnosed as IRRs by investigators and all associated signs and symptoms will be reported on a separate case report form with individual severity grading and timing for each sign/symptom. Only the IRR diagnosis will be reported on the AE case report form. Severity grading for the IRR itself will also be recorded in accordance with CTCAE V5.0. Dose modification guidance will be based on the reported severity of the IRR and not the signs and symptoms. Only drug-related reactions should be classified as IRRs.

There is no need for expedited reporting or use of complementary pages to report AESI, unless it meets the criteria for an SAE.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

<u>Collection of Pregnancy Information</u>

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

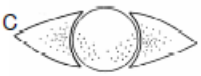
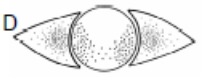
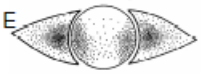
Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents of the neonate, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

See Section 6.6.

10.6 Appendix 6: Oxford Schema

<table>
<tr><td>DEWS</td><td>DRY EYE: DIAGNOSTIC TEST TEMPLATE</td><td></td></tr>
<tr><td>RAPPORTEUR</td><td>A.J.Bron</td><td>21st Oct 2004</td></tr>
<tr><td>TEST</td><td>Grading staining: Oxford Schema</td><td></td></tr>
<tr><td>TO DIAGNOSE</td><td>The scheme is used to estimate surface damage in dry eye.</td><td>REFERENCES</td></tr>
<tr><td>VERSION of TEST</td><td>[V 1]</td><td></td></tr>
<tr><td>DESCRIPTION</td><td>Surface damage to the exposed eye, assessed by staining, is graded against standard charts.</td><td></td></tr>
<tr><td>NATURE of STUDY</td><td>N. A.</td><td></td></tr>
<tr><td>CONDUCT of TESTS</td><td>Grading Schema:
Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale
<table>
<tr><th>PANEL</th><th>GRADE</th><th>CRITERIA</th></tr>
<tr><td>A  </td><td>0</td><td>Equal to or less than panel A</td></tr>
<tr><td>B  </td><td>I</td><td>Equal to or less than panel B, greater than A</td></tr>
<tr><td>C  </td><td>II</td><td>Equal to or less than panel C, greater than B</td></tr>
<tr><td>D  </td><td>III</td><td>Equal to or less than panel D, greater than C</td></tr>
<tr><td>E  </td><td>IV</td><td>Equal to or less than panel E, greater than D</td></tr>
<tr><td>>E</td><td>V</td><td>Greater than panel E</td></tr>
</table>
Conduct of Test:
• Dye is instilled.
• Slit-lamp is set (eg.16 magnification with x10 oculars with Haag-Streit).
• Cornea: The upper eyelid is lifted slightly to grade the whole corneal surface,
• Conjunctiva: To grade the temporal zone, the subject looks nasally; to grade the nasal zone the subject looks temporally.
• (The upper and lower conjunctiva can also be</td><td>Bron Evans Smith 2003.</td></tr>
</table>

	graded). **Selection of dyes:** A list dyes and filters can be found in the original paper. With fluorescein, staining must be graded as quickly as possible after instillation, since the dye then diffuses rapidly into the tissue and its high luminosity blurring the stain margin. Staining after rose bengal or lissamine green, persists at high contrast and may therefore be observed for a considerable period. This is convenient for both grading and photography. **Fluorescein sodium** **1. Quantified drop instillation** eg 2 µl of 2 % sterile fluorescein instilled into each conjunctival sac with a micro-pipette (using a sterile tip). In very dry eye, larger volumes risk the possibility of inadequate dilution into the fluorescent range. **2. Unquantified instillation – impregnated paper strips** This is a convenient approach in the clinic using the following method of application: • A single drop of unit dose saline is instilled onto a fluorescein-impregnated strip. • When the drop has saturated the impregnated tip, the excess is shaken into a waste bin with a sharp flick. • The right lower lid is then pulled down and the strip is tapped onto the lower tarsal conjunctiva. A similar procedure is carried out on the left. If too large a volume is delivered then the concentration in the tear film will be too high, and the tear film and staining pattern will be non-fluorescent. **3.Timing** The fluorescein break-up time (FBUT) is usually performed prior to grading. Since fluorescein diffuses rapidly into tissues, punctate staining blurs after a short period. It is therefore essential to assess staining rapidly, in sequence, in the right and then the left eye, so that the staining patterns observed are equally crisp. If it is intended to photograph the staining pattern for grading, then photography should follow immediately after each instillation. **Exciter and Barrier Filters** The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm A suggested filter pair for detection of fluorescein staining is a yellow, Kodak Wratten 12 barrier filter (transmitting above 495 nm) or an orange Wratten 15 filter (transmitting above 510 nm) in combination with a blue Wratten 47 or 47A exciter filter. The 47A shows greater transmittance than the Wratten 47 over the absorption range. The 'cobalt' filter of many slit-lamps is suitable to use with a Wratten 12 or 15	

	barrier. Where more light is required for photographic purposes, narrow band-pass, interference filters can be used. The use of both exciter and barrier filters allows both the cornea and conjunctiva to be assessed using a single stain. This is a major advantage in clinical trials where it is otherwise customary to employ fluorescein to grade corneal staining and rose bengal or lissamine green to grade conjunctival staining. **Disadvantages of Fluorescein Staining** Blurred pattern if reading is delayed. Delay in photographing fluorescein staining results in blurred images of the staining pattern. **Rose Bengal** The intensity of rose bengal staining is dose dependent. If drop size or concentration is reduced to minimize stinging, the amount of staining is also reduced. Use of impregnated strips will give weaker staining than use of a full drop of 1% solution. Best results are achieved with, eg. 25 µl 1%, instilled into the conjunctival sac. Because rose bengal stings, instillation is best preceded by a topical anesthetic. **Instillation Technique** 1) eg. A drop of Proxymetacaine is instilled into the conjunctival sac followed, after recovery, by; 2) A drop of rose bengal 1.0%. This is instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. 3) Since both anaesthetic and drop may stimulate reflex tearing, the test should follow measurement of the FBUT and of the Schirmer test. (Conjunctival staining due to insertion of the Schirmer paper can usually be distinguished from that due to dry eye disease). Both eyes may be stained prior to grading, since there is no risk of the staining pattern in the first eye being obscured by the time the second eye is graded. The cited paper gives advice about avoidance of overspill. **Visibility** Rose bengal staining on the conjunctiva shows up well against the sclera and may be enhanced using a red-free (green) light source. Corneal staining may show up well against a blue iris, but is difficult to see against a dark brown iris. **Phototoxicity** Photo-activation of rose bengal by sunlight increases post-instillation symptoms, especially in severe dry eye with heavy staining. This post-instillation pain can be minimised	

<table>
<tr><td></td><td>by liberal irrigation with normal saline at the end of the test.

Lissamine green stains the eye in a similar manner to rose bengal but is as well tolerated as fluorescein. Visibility and dose-dependency are the same as rose bengal and staining is persistant so that photography need not be performed immediately after instillation.
Lissamine green is available as impregnated strips or may be ordered as a pre-prepared solution. A 25 µl 1% drop will give more intense staining. Because the drop is well tolerated, no anaesthetic is required.

Visibility
As with rose bengal, lissamine green staining is easily visible on the conjunctiva. On the cornea, staining is seen well against a light blue iris background but is poorly visible against a dark brown iris background. For both rose bengal and lissamine green, because the dyes are poorly seen within the tear film, the dye in the tear film does not obscure the staining pattern. Also, since both dyes do not diffuse into the substantia propria of the conjunctiva, the staining pattern is retained for longer.

Visibility of staining may be enhanced using a white light source and a red barrier filter, to give a black pattern on a red ground. A suitable filter is a Hoya 25A, or a Kodak Wratten 92.</td><td></td></tr>
<tr><td>Web Video</td><td>Not available</td><td></td></tr>
<tr><td>Materials:</td><td>Oxford Grading Charts - available from A J Bron anthony.bron@eye.ox.ac.uk</td><td></td></tr>
<tr><td>Standardization</td><td>Nil additional</td><td></td></tr>
<tr><td>Variations of technique</td><td></td><td></td></tr>
<tr><td>Diagnostic value</td><td>No stats supplied.</td><td></td></tr>
<tr><td>Repeatability</td><td>A small intra-interobserver study was carried out in 1986 and was presented but not published:

Intra-observer study: This study asked two trained ophthalmologists to grade a series of standard slides, showing corneal and conjunctival fluorescein staining, on 2 separate occasions. [note: -this study is only relevant to grading photographic records not patients.]

Intra-observer κ for grading photographs of staining, using the Oxford scheme. Two observers.
<table>
<tr><td></td><td>Cornea</td><td>Conjunctiva</td></tr>
<tr><td>Observer 1</td><td>0.86</td><td>0.69</td></tr>
<tr><td>Observer 2</td><td>0.65</td><td>0.83</td></tr>
</table>
Not that values are in the good to excellent range.

Inter-observer study: In this study, the same 2 observers</td><td>Hardman Lea et al. 1986 AER abstract.</td></tr>
</table>

<table>
<tr><td></td><td>graded fluorescein staining (blue exciter; yellow filter) in 13 dry eye patients at an interval within 2-3 weeks.

Inter-observer κ for grading patients with dry eye, using the Oxford scheme. Two observers. Fluorescein; bengal rose
<table><tr><td>Observer 1 v 2</td><td>Cornea</td><td>Conjunctiva</td></tr><tr><td>Fluorescein</td><td>0.88</td><td>0.48</td></tr><tr><td>Bengal rose</td><td>0.87</td><td>0.54</td></tr></table>
It is of interest that observations are in the excellent category for cornea, with either stain and in the fair category for conjunctiva.</td><td></td></tr>
<tr><td>Sensitivity</td><td>(true positives) [-]</td><td></td></tr>
<tr><td>Specificity</td><td>(100 – false positives) [-]</td><td></td></tr>
</table>

Source: See Reference (4).

10.7 Appendix 7: Abbreviations

List of abbreviations

ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special safety interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C1D1	Cycle 1 day 1
CDL	Clinical Development Leader
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of federal regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
ECG	Electrocardiogram
eCRF	Electronic case report form
e.g.	For example
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FSH	Follicle stimulating hormone
FU	Follow-up
GCL	Global Clinical Leader
GCP	Good clinical practice
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRR	Infusion-related reactions
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IxRS	Interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NA	Not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-investigational medicinal product
OS	Overall survival
PK	Pharmacokinetics
Q3W	Every 3 weeks
QT	Q wave T wave

QTcB	Corrected QT using Bazett's formula
QTcF	Corrected QT using Fridericia's formula
RBC	Red blood cell
ROS	Rollover study
SAE	Serious adverse event
SAP	Statistical analysis plan
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SOC	Standard of care
SPK	Superficial punctate keratitis
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TOC	Table of contents
US/ USA	United States/ United States of America
WBC	White blood cell
WOCBP	Women of childbearing potential

10.8 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (10 JAN 2019)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Title Page	EudraCT number was updated.	A change in sponsorship requires a new EudraCT number for this study.
10.2 Appendix 2: Clinical Laboratory Tests	Direct bilirubin was removed.	Correction of an inconsistency between Schedule of Activities and Appendix 2 Clinical Laboratory Tests.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

11. References

1. Morello A, Sadelain M, Adusumilli PS. Mesothelin-Targeted CARs: Driving T Cells to Solid Tumors. Cancer Discov. 2016;6(2):133-46.
2. Tang Z, Qian M, Ho M. The role of mesothelin in tumor progression and targeted therapy. Anticancer Agents Med Chem 2013;13(2):276-80.
3. Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. Clinical & translational immunology. 2015;4(7):e39.
4. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea. 2003;22(7):640-50.