Title of the clinical study:

Prophylactic **I**ntravitreal 5-Fluorouracil and Heparin to Pre**vent** PVR in High-risk Patients with Retinal Detachment.

Investigational medicinal product: 5-Fluorouracil and low molecular weight heparin

Eudra-CT number: 2015-004731-12

Register-number: Clinical Trials.gov Identifier: NCT02834559.

Short description: PRIVENT

Clinical study report (Summary)

(Final) V1_0/ Date: 2022-06-14

Sponsor of the clinical study:

University of Cologne, Albertus-Magnus-Platz, 50923 Cologne, Germany

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Start of the study – Completion of the study

First patient enrolled: 22.11.2016
Last patient last randomized: 12.03.2020
Last patient last visit: 04.06.2020

Signatures

The signing authors agree with the contents of the present final clinical study report through their signatures. The clinical study reported here has been conducted according to the Declaration of Helsinki, the good clinical practice guidelines as well as the relevant legal requirements.

Sponsor's qualified person/ Coordinating investigator		Köln, 15.06.2022
	PD Dr. Friederike Schaub	Place, Date
Statistician		
	Dr. Petra Schiller	Place, Date
If applicable, further authors of the result report		
	Name, Title	Place, Date

Signatures

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Sponsor's qualified person/ Coordinating investigator	PD Dr. Friederike Schaub	Place, Date
Statistician	Dr. Petra Schiller	Köln, 14.6.22 Place, Date
If applicable, further authors of the result report	Name, Title	Place, Date

Title of the study	**Pr**ophylactic **I**ntravitreal 5-Fluorouracil and Heparin to Pre**vent** PVR in High-risk Patients with Retinal Detachment.
Amendments	Amendment Study Protocol (V03_0 of 30.07.2019) and patient informed consent form: due to change of the principle coordinating investigator, approved: 16.08.2019
Statistical analysis plan	PRIVENT_SAP_V01_2019-11-26 (finalized before interim analysis) and PRIVENT_SAP_V02_2021-05-06 (update, finalized before final analysis)
Nature of the project	Clinical study according to AMG of the phase III. A randomized, double blind, controlled, multicentre, interventional trial with one interim analysis.
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Publication of the study (Reference)	**Schaub F**, Hoerster R, Schiller P, Felsch M, Kraus D, Zarrouk M, et al. Prophylactic intravitreal 5-fluorouracil and heparin to prevent proliferative vitreoretinopathy in high-risk patients with retinal detachment: study protocol for a randomized controlled trial. Trials. 2018;19(1):384. **Schaub F, Schiller P**, Hoerster R, Kraus D, Holz FG, Guthoff R, Agostini H, Spitzer MS, Wiedemann P, Lommatzsch A, Boden KT, Dimopoulos S, Bemme S, Tamm S, Maier M, Roider J, Enders P, Altay L, Fauser S, Kirchhof B, for the PRIVENT Study Group. Intravitreal 5-Fluorouracil and

	Heparin to Prevent Proliferative Vitreoretinopathy: results from a randomized clinical trial. Ophthalmology. 2022, accepted
Study period	Date of the first included subject: 22.11.2016 Date of the last visit of the last included subject: 04.06.2020. The study was terminated prematurely in accordance with the recommendations of the Data Monitoring and Safety Committee (DMSC). The decision was made on the basis of the insignificant results of the interim analysis (no chance to show the expected effect even with complete recruitment).
Study objectives	Proliferative vitreoretinopathy (PVR) is a common cause for postoperative failure after vitreoretinal surgery for primary rhegmatogenous retinal detachment (RRD). There is no standard-therapy to prevent PVR. Several attempts using chemotherapeutic agents like 5-fluorouracil (5-FU) with low molecular weight heparin (LMWH) or daunomycin have been undertaken to prevent this proliferation-process, but none of these was introduced into routine clinical practice. Until recently, it has been challenging to identify patients with high risk for postoperative PVR formation. This is especially important, because potentially harmful chemotherapy should be used only in high-risk eyes. For several years, non-invasive laser-flare photometry has been established as a tool for fast and precise estimation of high-risk patients for PVR re-detachments. The COCHRANE-collaboration has recently reviewed two independent randomized, controlled trials using 5-FU and LMWH to prevent PVR. As a consequence, the use of 5-FU and LMWH in a randomized, controlled trial in high-risk patients was recommended.[1] The objective of the present trial was the reduction of the incidence of PVR in high-risk patients with primary rhegmatogenous retinal detachment (RRD) by intraoperative adjuvant therapy with 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH). The elevated risk for PVR development was determined by laser flare photometry (elevated protein levels in the anterior chamber fluid; objective tyndallometry).
Primary Outcome	PVR grade CP 1 or higher [yes/no] within 12 weeks assessed by an Endpoint Committee (EPC). Explanation: PVR usually develops within 6-8 weeks postoperatively. In order to reliably uncover all cases with the development of a PVR, the time frame was set to 12 weeks. PVR grade CP 1 or higher was explicitly chosen as primary outcome variable because this is an indication for renewed surgical intervention.
Secondary Outcomes	• PVR grade CP 1 or higher [yes/no] within 6 weeks • PVR grade CA 1 or higher [yes/no] within 6 weeks and 12 weeks • Degree of PVR (PVR grade CA 1-12, PVR grade CP 1-12 (in clock hours)) within 6 weeks and 12 weeks • Best corrected Visual Acuity (BCVA) measured by ETDRS charts within 6 weeks and 12 weeks • Retinal reattachment after primary intervention [yes/no] after 6 weeks and 12 weeks • Number of retinal re-detachment and if present due to PVR [yes/no] within 6 weeks and 12 weeks

	• Number and extent of surgical procedures necessary to achieve retinal reattachment within 12 weeks • Occurrence of at least one drug-related adverse event with effect on the study eye [yes/no] within 12 weeks Explanation: The functional and safety-relevant variables also were recorded, as well as the occurrence of any form of PVR.
Study design	• Study Design: Randomized, controlled, double blind, multicenter trial with one interim analysis. • The relevant difference to previous studies on the effectiveness of 5-FU and heparin in PVR is that a prophylactic instead of therapeutic approach was chosen here. Only high-risk patients were included. Furthermore, the PRIVENT trial is the first German trial on this topic with multicenter design. • Treatment groups: 5-fluorouracil and low molecular weight heparin (Verum) were examined in comparison to Placebo (Balanced salt solution) in a 1:1 randomized design: (A) Verum: Intraoperative adjuvant application of 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH) via intraocular infusion during routine pars plana vitrectomy (PPV) in high-risk patients for PVR with primary rhegmatogenous retinal detachment (RRD). Versus: (B) Placebo: Routinely used intraocular infusion with balanced salt solution (BSS) during routine PPV. • Randomization: Patients were assigned to treatment arms (1:1) by means of the central 24-7 internet randomization service ALEA. The randomization was stratified by surgeon. • Blinding: The pharmacy provided numbered medication kits for Verum and Placebo designed in equal manner. ALEA assigned patients to this numbered medication kits; thus, allocation was concealed and patients and investigators were fully masked regarding trial treatment. Unblinding was only performed in case of a Suspected Unexpected Serious Adverse Event (SUSAR). • Patient population: Planned: 560 patients (280 per arm), randomized patients: 326 (see Figure 1: Recruitment). • Randomized patients underwent the following visits: Visit 1: Baseline; Visit 2: Surgery; Visit 3: Visit between postoperative days 1 to 5; Visit 4: First follow-up visit 6 weeks ±10 days postoperatively; Visit 5: Close-out visit 12 weeks ±10 days postoperatively (final examination). Only in case of any necessary revision surgery: Visit 1.x: Re-admission; Visit 2.x: Re-surgery; Visit 3.x: Re-discharge Visit (between postoperative days 1 to 5) (see Appendix, Figure 2: CONSORT trial flow chart). • A planned interim analysis was performed after 280 included patients (see Appendix, Figure 1: Trial sequence).

	• An Endpoint Committee (EPC) has been established in order to evaluate the incidence of the primary endpoint according to the classification of retinal detachment with proliferative vitreoretinopathy. Primary endpoint (PVR grade CP 1 or higher [yes/no]) as well as selected secondary endpoints (degree of PVR (CA 1-12 and/or CP 1-12 (clock hours)), and retinal attachment at the specific time points) were assessed and evaluated by the endpoint committee based on fundus photos. Fundus photos were taken in 9 gaze directions during visit 4 and 5. Two members of the committee judged each single photo and documentation of revision surgery on applying the endpoints. In case of disagreement, a third member was involved in the decision-making. • A Data Monitoring and Safety Committee (DMSC) made up of independent experts had been set up. It consisted of two physicians and a statistician who were not involved in the conduct of the trial. The task of the DMSC was to oversee the safety of the trial subjects in the clinical trial by periodically assessing the safety of the trial therapy. Throughout this process of surveillance, the DMSC provided the sponsor with recommendations with regard to continuing the trial (e.g. termination or modification) based on the data collected.
Investigational medicinal product(s)/ treatment strategy	IMP: 5-Fluorouracil and low molecular weight heparin (LMWH). The intervention comprised a standard-of-care 3 port pars plana vitrectomy with intraocular infusion containing the IMP. The trial drugs were delivered in two amber glass vials for injection in a stock concentration of 100mg/2ml 5-FU and 2500IU/1ml Dalteparin. Both were injected in a 500ml bottle Balanced Salt solution for intraocular infusion. The concentration of 5-FU and LMWH in 500 ml BSS was 200µg/ml and 5IU/ml. IMP was stored at room temperature (15 – 25°C) in the trial site. (Arm 5-FU and Dalteparin is referred to as Verum or Arm V)
Treatment/ Intervention	Intraoperative adjuvant application of 5-FU and LMWH via intraocular infusion during routine pars plana vitrectomy (PPV) in patients with primary RRD versus routinely used intraocular infusion with buffered saline solution (BSS) during routine PPV. The duration of trial drug application was ≤ 60 minutes.
Comparing condition/medical preparation	Balanced salt solution (BSS) served as Placebo. BSS equally packaged as Verum served as Placebo to provide blinding of the trial. Usage of Placebo was justifiable as no standard treatment for PVR-prevention exists. Placebo was delivered in two amber glass vials for injection: 1-2 ml Balanced Salt Solution (BSS). Both were injected in a 500ml bottle Balanced Salt solution for intraocular infusion. Storage was at room temperature (15 – 25°C). (Arm Placebo is referred to as Placebo or Arm P)

Total number of study participants	Number prescreened patients: n = 3047 Number enrolled patients: n = 326 Number randomized: n = 326 Number drop-outs: n = 37 560 patients were planned to be assigned. An interim analysis was performed after the first 280 patients and the study was prematurely terminated after 326 patients according to the recommendation of the endpoint committee (see appendix, Figure 1: Trial sequence).
Study population	**Analysis sets:** The primary analysis set was the modified intention-to-treat (mITT) population. It included all enrolled and randomized patients who received the initial surgery and application of 5-FU and Dalteparin (Verum; n=163) or Placebo (n=162, see Figure 2: CONSORT Flow Diagram). Patients were analysed in the assigned treatment groups regardless of the actual received treatment (in two cases, kits were mixed-up, but no switches between groups occurred, see Appendix 6b_Analysis_sets, Table 19). The secondary analysis set was the per-protocol set (PPS). It included all patients who received the trial intervention and application of Verum (n=123) or Placebo (n=127) as assigned, who were treated and observed according to protocol and who had no major protocol violations (definition and procedure is given in the SAP). In total, 75 patients were excluded from the PP-set, 40 in Arm V and 35 in Arm P. Prior to interim as well as final analyses a blind review of all protocol violations was done by the lead investigator, to state, which deviation would result in exclusion of one of the analysis sets. Numbers of drop-outs and reasons are given in the CONSORT flow diagram (Figure 2). One patient (randomized to Placebo) did not receive IMP and therefore was excluded from the modified ITT set as well as from the safety set. An overview of the reasons for exclusion is provided in the appendix 6b_Analysis_sets, table 20. Most of the cases related to 'premature discontinuation' (n=36; V: n=23, P: n=13), followed by 'primary endpoint not assessable by EPC' (n=15; V: n=6, P: n=9) and 'incorrect timing of FU3' (n=13; V: n=4, P: n=9). Further reasons for exclusion were related to inclusion/exclusion criteria (n=7), surgery (n=1) or IMP (n=3). Further details including a listing of all patients excluded from the PPS are also given in the appendix 6b_Analysis_sets, table 21. The safety population included all 325 randomized patients who were operated and received Verum (n=163) or Placebo (n=162). Analysis was according to the treatment received. **Protocol deviations:** In total, 336 protocol deviations were reported by monitor or data manager (V: n=177; P: n=159), 178 were assessed to be possibly major (V: n=94; P: n=84). These protocol deviations occurred in 175 patients (V: n=92; P: n=83), mostly one or two deviations per patient were reported (n=129), but in some individual cases up to 6 or 7 deviations were stated (a listing of all individual protocol deviations is given in appendix 6b_Analysis_sets, table 29). Preliminary remarks on the results presented: In the synopsis we mainly focus on the results obtained from the analysis sets which were derived from the total group of randomized patients (that is, due to the shortening of the second stage, both stages were analysed together). Results for demography and key endpoints separated by stage are given

	in the respective appendices (example: 6a_female_Demography, table 3 contains the results for women of stage 1, table 4 for women of stage 2, etc.).
Inclusion criteria	• Primary rhegmatogenous retinal detachment (<4 weeks) in study eye • Scheduled for pars plana vitrectomy for retinal detachment repair without combined cataract surgery • Elevated protein levels in anterior chamber fluid (laser flare value ≥ 15 pc/ms) in study eye • Male and female patients ≥ 18 years of age • Written informed consent
Exclusion criteria	• Participation in another trial of IMPs or devices parallel to, or less than 3 months before screening, or previous participation in this trial. • Known to or suspected of not being able to comply with the protocol. • Positive urine pregnancy test, pregnancy or breastfeeding mother. • Evidence or history of alcohol, medication or drug dependency within the last 12 months. • Evidence or history (within the last 12 months) of neurotic personality, psychiatric illness that requires or required treatment, epilepsy or suicide risk. • Women of child bearing potential without satisfactory contraception, i.e. hormonal contraceptives for at least 7 days before trial enrolment, IUD, double barrier (women of child bearing age must be counselled about the use of adequate contraception). • Any dependency of the patient to the Investigator or the trial site, e.g. employees with direct involvement in the proposed trial or in other trials under the direction of this Investigator or trial site, as well as family members of the employees or the Investigator. • Inability to understand the rationale of this trial or the study aim • Manifest uveitis in study eye • Active retinal vascular disease in study eye • Chronic inflammatory conditions in study eye • Endophthalmitis in study eye • Aphakia in study eye • Uncontrolled glaucoma in study eye (intraocular pressure ≥ 30 mmHg) • Perforating and non-perforating trauma in study eye • Proliferative diabetic retinopathy in study eye • Retinal dystrophies in study eye • Malignant intraocular tumor in study eye • Previous intraocular surgery except uncomplicated cataract surgery with posterior chamber lens implantation in study eye • Cataract surgery in study eye ≤ 3 months ago • Scheduled for combined pars plana vitrectomy and cataract surgery for retinal detachment repair in study eye • Previous retinal procedures (laserpexy, cryopexy, intravitreal gas-injection, anti-VEGF or corticosteroid-injection) in study eye ≤ 6 months • Giant retinal tears in study eye (size > 3 clock hours) • Traumatic retinal detachment in study eye • Retinal detachment lasting > 4 weeks in study eye

	• Visual pre-existing PVR grade C in study eye • Other uncontrolled ophthalmologic disorders • Single eyed patients (BCVA of fellow eye > 1.0 log MAR, < 0.1 decimal, < 1/10 tenth, or < 6/60 Snellen fraction [m]) • Systemic disorders not compatible with adjuvant application of 5-FU and LMWH via intraocular infusion, or not compatible with the local or general anesthesia • Any therapy with immunosuppressant or chemotherapy ≤ 3 months and during the trial period
Description of demography and baseline characteristics	325 subjects (mITT) had been enrolled, randomized and received the initial surgery and application of 5-FU and Dalteparin (n=163) or Placebo (n=162). Mean age was 65 ± 10 years (74% males, 54% right eyes). Mean laser flare value was 31 ± 26 pc/ms, 65% of included eyes were pseudophakic and 35% were phakic. In 68% the macula was detached and mean visual acuity prior to surgery was 1.0 ± 0.7 logMAR. Table 1 in Appendix summarizes demographics and baseline characteristics for the total study cohort and both arms in detail (modified ITT set). Further details on demographics, vital signs and ophthalmological examination (including comments) at baseline are given in appendix 6a_Demography. Moreover, information on medical history is given in appendices 6c_Medical history and the related parts (results separated by analysis population and sex). The per protocol set (PPS) comprises n=250 (5-FU and Dalteparin: n= 123; Placebo: n=127) with mean age 64 ± 9.4 years, 78% were male, 56% right eyes. 34% of eyes were phakic, macula was detached in 66% (see Appendix 6a_PP_Analysis_demography). Details for subgroups are given in the appendices (6a_female_Demography, 6a_male_Demography and 6a_PP_female_Demography, 6a_PP_male_Demography).
Description of Efficacy	The IMP (composed of 2 components) under evaluation in this trial was 200µg/ml 5-FU and 5IU/ml LMWH in Balanced Salt Solution (BSS). The IMP components, either two Verum components (5-FU and LWMH) or two Placebo components (BSS), were injected in the 500 ml intraocular infusion (BSS) in order to constitute the IMP for intravitreal application during pars plana vitrectomy. This ocular irrigating solution was used only one time (time of primary retinal re-attachment surgery) and according to standard format of the surgical procedure. Since the IMP was only applied once during retinal re-attachment surgery, no compliance assessment was necessary. **Description of surgery and drug application:** The average duration of the complete surgery was 40.5 min (Verum) or 38.9 min (Placebo), respectively, duration of study drug application was 23.3 min in both groups. The end volume of the infusion bag differed individually, but distribution was balanced in both groups. Details on surgery and exposure to treatment like duration of infusion and end volume of infusion bag are summarized in appendix 6d_Analysis_exposition_of_ treatment. A listing of the individual quantity is given, too.

Results of interim analysis: A pre-planned interim analysis was performed after 280 (50% of planned patient) patients were included. The primary endpoint (PVR grade CP1 or higher within 12 weeks [yes/no]) was assessed by the EPC using uploaded fundus photos. In total, 215 patients were assessed to have no PVR-grade CP, 26 patients showed PVR grade CP1 or higher (13 in each arm), and 39 were evaluated as 'not assessable' (Verum: 23, 16.3%; Placebo: 16, 11.5%; mITT).

PVR grade CP 1 or higher (EPC assessment)	Total (n=280)	Verum (n=141)	Placebo (n=139)
yes	26 (9.3%)	13 (9.2%))	13 (9.4%)
no	215 (76.8)	105 (74.5%)	110 (79.1%)
not assessable	39 (13.9%)	23 (16.3%)	16 (11.5%)

The EPC stated the following reasons for 'not assessable': not assessable due to poor quality in one case and photos not done in 38 cases (of which 12 were lost, 10 withdrew consent or had other reasons for premature discontinuation. Patients who discontinued early or were lost to follow-up within 12 weeks after surgery and/or who could not be assessed by EPC due to lack of information on PVR status were counted as treatment failures in the primary analysis.)

The confirmatory analysis (mITT set) resulted in a p-value of 0.385 (Mantel-Haenszel test accounting for stratification by surgeon, asymptotic 2-sided; the results were confirmed by the analysis of the per-protocol set, p-value 0.930). Thus, the p-value was above the O'Brien and Fleming boundary of 0.0052. Therefore, the stopping criteria was not fulfilled. Stopping for futility was not intended in the protocol, but assessment of the conditional power showed a very low chance to reach a p-value for stage 2 (a number of additional 280 patients would provide a power of 21.3% (uncorrected Chi^2-test; or 18.7% Fisher's exact test)), so that the combination of p-values would give a final p-value equal or below the predefined boundary of 0.048.

The safety results of both groups did not indicate any safety concern.

Based on the results of the interim analysis and in view of the recruitment that had been much slower than expected, the DMSC recommended early termination of the trial and the trial was stopped on 13th of March 2020.

Results of final efficacy analysis: 118 of 163 patients (72%) in Verum arm and 124 of 162 patients (77%) in Placebo arm showed no PVR grade CP within 12 weeks after initial surgery. Overall, 83 cases were counted as failures, including cases which were not assessable by the EPC (45 (28%) in Verum arm and 38 (23%) in Placebo arm; mITT).

The overall result in terms of odds ratio (Verum to Placebo) was 1.25 (95%-confidence interval: 0.76 to 2.08; p-value 0.77, result for all trial

patients including overrunning patients, mITT; findings separated by stage are given in Table 2 in the appendix).

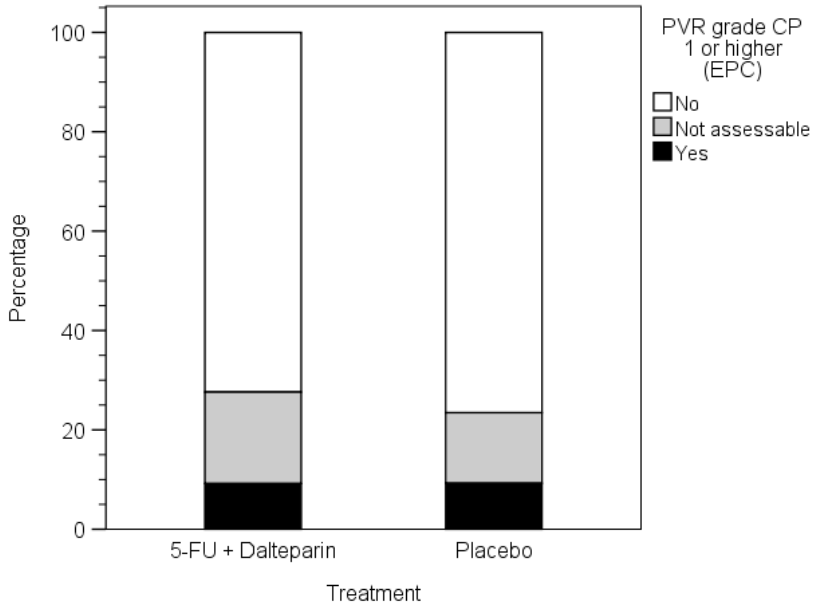


Figure 4: Primary endpoint: results of assessment by EC

The non-assessable cases accounted for 16% (30/163 or 19% in Verum arm, 23/162 or 14% in Placebo). That resulted in 15 cases (9%) of confirmed PVR grade CP1 or higher in each group (see Figure 4 and Table 2).

Above all, cases were not assessable because photos were not done due to premature discontinuation of patients (Verum: 23/30; Placebo: 13 / 23, Table 2).

Per-protocol analysis confirmed the results (OR: 1.05, 95%-CI 0.47 to 2.34, p-value 0.47).

A summary of the results of secondary endpoints is given in Tables 3a – c. None of the secondary endpoints show any significant difference between treatment groups. Visual acuity showed a significant improvement from baseline to week 12 in each group, but no difference between Verum and Placebo arm (mean difference: 0.03, 95%-CI: -0.05 to 0.11; p-value = 0.44).

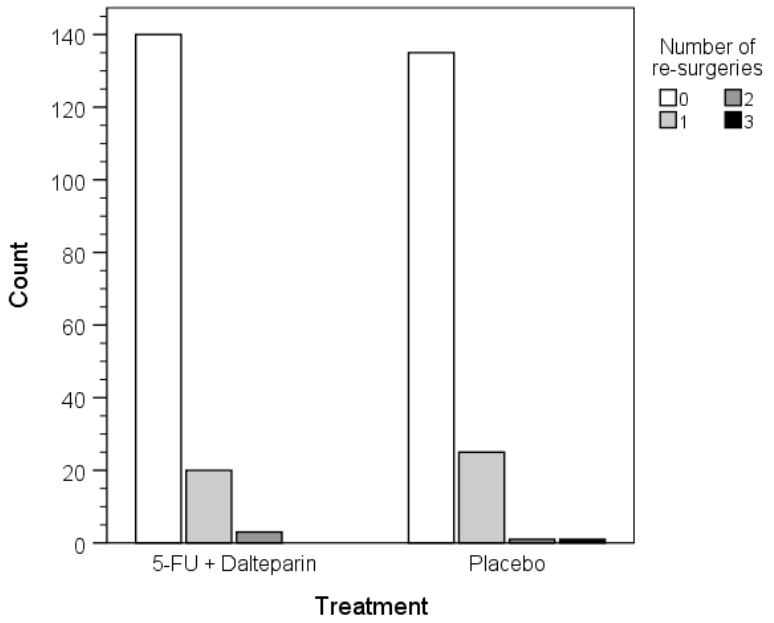


Figure 5: Number of re-surgeries

Re-surgeries were rare, 11 patients in Verum arm and 14 in Placebo arm needed a re-surgery to achieve retinal re-attachment (2 or 1 patient, respectively, needed 1 or 2 subsequent re-surgeries until; two other patients in Placebo arm got a re-surgery but could not achieve re-attachment). Further details on primary and secondary endpoints including results of subgroup analyses is given in the appendices 6h_Analysis_Primary endpoint to 6i_PP_male_Analysis_Secondary endpoints. Additional information on re-surgeries is shown in 6j_Analysis_re-surgeries.

Description of Safety

The maximum allowed time of intravitreal application of the IMP was 60 minutes and the maximum volume was 500ml of the composition. The IMP did not remain in the vitreous cavity, but was washed out in all cases independent of endotamponade chosen by the surgeon.

During the study period no unexpected potentially safety issues appeared. The IMP application had been tolerated well. No significant safety risks were identified.

Adverse events (AE) and serious adverse events (SAE): In total 1457 AEs and thereof 89 SAEs had been reported (Verum: 42 SAEs and 670 AEs; Placebo: 47 SAEs, 698 AEs; see appendix Table 4a). 1254 AEs (thereof 73 SAEs) were related to the study eye, 27 AEs (thereof 1 SAE in Verum arm) were both, study-eye related as well as drug-related (Verum: 14, Placebo: 13, Table 4b). There was no difference between both arms.

Table 4b: Number of (S)AEs related to study eye and related to study medication (unit of observation: event); preferred term category by received treatment

Relatedness to study medication	Preferrred term (category)	Total	Received treatment 5-FU + Dalteparin	Placebo
SAE				
Possible	Vitreo-retinal disorders	1	1	0
AE				
Probable/likely	Cataract and irritation of natural lens	1	0	1
	Vitreo-retinal disorders	1	1	0
	Total	2	1	1
Possible	Intraocular inflammation	6	1	5
	Reduced visual acuity	1	1	0
	Irritation of conjunctiva and/or cornea	3	2	1
	Cataract and irritation of natural lens	2	2	0
	Vitreo-retinal disorders	2	1	1
	Choroidal haemorrhage	1	1	0
	Intraocular haemorrhage	1	1	0
	Intraocular pressure decompensation	5	2	3
	Total	21	11	10
Conditional / unclassified	Vitreo-retinal disorders	1	0	1
	Total	1	0	1
Unassessable / unclassifiable	Irritation of conjunctiva and/or cornea	1	1	0
	Vitreo-retinal disorders	1	1	0
	No eye disorder	1	0	1
	Total	3	2	1
All (S)AEs related		**27**	**14**	**13**

Note: Database export of 2020-12-04, MedDRA coding of 2020-12-04

Table 4c and 4d summarize the findings on the relationship of events to study procedure or study medication and the outcome of AEs and SAEs. By far the most patients recovered from SAE or AE. From 89 SAEs a number of 62 were assessed as recovered / resolved or recovering / resolving, 24 were resolved with sequelae (17 vitreo-retinal disorders, 1 intraocular pressure decompensation, 6 non-eye disorder). One patient died from a cardiac failure (Verum arm, not related to medication or procedure, see below), two SAEs were not resolved and were ongoing at the end of the study (2 vitreo-retinal disorders, relationship to study medication unlikely, one in each arm; outcome of AEs see Table 4c and 4d). Additional information is provided in further summary tables and detailed listings of all SAEs, AESIs, SUSARs and AEs (see Appendix 6f_Adverse_events).

Adverse events of special interest (AESI): A lack of recovery of visual acuity (BCVA) to 0.3 log MAR/ 0.5 decimal or better and/or decrease of visual acuity (BCVA) to > 0.3 log MAR/< 0.5 decimal (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour during the postoperative course without morphological correlate in study eye that presented with primary rhegmatogenous retinal detachment with macula on status prior to surgery was defined as an AESI. During the follow-up time only one AESI occurred (Verum arm, see Table 4a, subsector AEs related to study eye and 6f_Analysis_adverse_events, Table 35).

Suspected unexpected serious adverse reactions (SUSAR): Only 1 SUSAR was reported (macular hole in study eye, 66 yrs, male).

	The respective patient received according to the study protocol 200ml of IMP (which included 40mg of 5-Fluorouracil and 1000 IU Dalteparin (LMWH) in balanced salt solution). The route of IMP administration was intraocular during pars plana vitrectomy over a period of 40 minutes. Postoperatively the investigator became aware of a macular hole in the study eye with severity of CTC-grade 3. The event was reported as serious adverse event. The investigator assessed the event as possible related to 5-Fluorouracil, Dalteparin, or Placebo and as possible related to the investigational procedure (pars plana vitrectomy for primary rhegmatogenous retinal detachment repair). A revisional surgery was planned for surgical treatment. Nevertheless, the scheduled pars plana vitrectomy was cancelled because of recovery of the macular hole without treatment. Outcome of the event was documented finally as recovering. **Deaths:** One patient who was treated in the Verum arm died from cardiac failure (90 yrs, female). The event was assessed as not to be related to medication or trial procedure.
Statistical methods:	**Interim analysis:** After half of the planned number of patients were randomized (i.e. 280 out of 560) a pre-planned interim analysis was done. Recruitment, patient characteristics, safety (AEs and SAEs), primary endpoint (PVR grade CP 1 or higher within 12 weeks [yes/no]) and the BCVA (secondary endpoint) were described. The incidence of PVR grade CP 1 or higher after 12 weeks was compared between the groups using the conservative boundaries of O'Brien & Flemming ($p \leq 0.0052$ for interim analysis and $p \leq 0.048$ for final analysis). For the calculation of p_2, the P value of the Mantel-Haenszel test at the second stage, only the data of the second stage will be used. The P value of the final analysis is calculated by combining the P values of both stages using the Inverse-Normal-Method by Lehmacher and Wassmer.[2] **Final analysis:** The primary endpoint of the trial is the occurrence of PVR grade CP 1 within 12 weeks. The null hypothesis H0 "the PVR grade CP 1 incidence is equal in both treatment groups (Verum, Placebo)" was tested by application of the Mantel-Haenszel test accounting for the stratification by surgeon. The primary analysis was performed using the modified ITT population (mITT). Missing values were assumed to be missing at random. For the primary analysis a missing primary endpoint was considered a treatment failure. Relative Risks (with confidence intervals and P values) were calculated for the overall effect between the trial groups and within the strata. Secondary endpoints were evaluated by descriptive methods. Numerical data were summarized by number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum; categorical data were summarized by number and percentage of patients. If P values were computed for the secondary parameters no adjustment for multiplicity and interim analyses has been done. Therefore, no confirmatory test decisions were possible with those P values. P values ≤ 0.05 (5%) were considered to be statistically important.

	For all primary and secondary parameters descriptive statistics were given overall and separated by treatment group. Moreover, results separated by stage are given in the respective appendices and table 2. The safety analysis was performed in the safety population. Analysis was according to the treatment received (as treated). Adverse events and serious adverse events were summarized by treatment group, MedDRA code (system organ class, preferred term), severity and relatedness. Summary statistics were grouped by treatment. Furthermore, safety parameters were listed by patient and treatment group. Subgroup analyses (demographic and baseline variables, efficacy endpoints) were done by sex and lens status (pseudophakic / phakic: see appendix). All statistical calculations were done with SPSS Statistics 26 (IBM Corp., Armonk, NY, USA).

Summary:

PVR is the major cause for postoperative failure after vitreoretinal surgery for primary rhegmatogenous retinal detachment. Adjunct pharmaceutical therapy was found to be ineffective, once PVR is established. Preliminary data suggested that prevention of PVR yields better functional outcome. So far there is no standard-therapy to prevent PVR.

The objective of the present trial was the reduction of the incidence of PVR in high-risk patients with primary rhegmatogenous retinal detachment (RRD) by intraoperative adjuvant therapy with 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH). The elevated risk for PVR development was determined by laser flare photometry.

325 subjects (mITT) in 13 German trial sites had been enrolled, randomized and received the initial surgery and application of 5-FU and Dalteparin (n=163) or Placebo (n=162). Mean age was 65 ± 10 years (74% male, 54% right eyes). Mean laser flare value was 31 ± 26 pc/ms.

A pre-planned interim analysis was performed after 50% of planned patient. No significant difference in relation to the primary endpoint could be revealed. Based on the results of the interim analysis and in view of the recruitment that had been slower than expected, the DMSC recommended early termination of the trial and the trial was stopped on 13th of March 2020.

Results Efficacy:

There was no significant difference in relation to the primary endpoint between the two treatment groups. 118 of 163 patients (72%) in Verum arm and 124 of 162 patients (77%) in Placebo arm showed no PVR grade CP within 12 weeks after initial surgery. Overall, 83 cases were counted as failures, including cases which were not assessable by the EPC (45 (28%) in Verum arm and 38 (23%) in Placebo arm; mITT). The overall result in terms of odds ratio (Verum to Placebo) was 1.25 (95%-confidence interval: 0.76 to 2.08; p-value 0.77, result for all trial patients including overrunning patients, mITT). Mostly due to a higher number of non-assessable patients in the verum arm, the PVR-CP-rate was higher than in the Placebo arm and consequently the odds ratio (V to P) was greater than 1.None of the secondary endpoints showed any significant difference between treatment groups. Visual acuity showed a significant improvement from baseline to week 12 in each group, but no difference between Verum and Placebo arm (mean difference: 0.03, 95%-CI: -0.05 to 0.11; p-value = 0.44).

Results Safety:

During the study period no unexpected potentially safety issues appeared. The IMP application had been tolerated well. No significant safety risks were identified.

In total 1457 AEs and thereof 89 SAEs had been reported (Verum: 42 SAEs and 712 AEs; Placebo: 47 SAEs, 745 AEs). 1254 AEs (thereof 73 SAEs) were related to the study eye, 27 AEs (thereof 1 SAE in Verum arm) were both, study-eye related as well as drug-related (Verum: 14, Placebo: 13). There was no difference between both arms.

One patient died from a cardiac failure (Verum arm, not related to medication or procedure, see above), two SAEs were not resolved during the follow-up time. Only one AESI and one SUSAR occurred.

Conclusion:

According to the results, the adjuvant therapy with 5-Fluorouracil and Dalteparin in eyes with primary rhegmatogenous retinal detachment and increased laser flare value does not seem to improve the PVR rate. Several reasons can be discussed why the results of the study did not meet the expectations. Until now a major problem has been to identify patients at risk for PVR in order to limit potentially harmful chemotherapy to high-risk patients only. High-risk patients for PVR have been so far determined in a complicated manner based on anamnestic risk factors such as diabetic retinopathy, accompanying uveitis, aphakia or penetrating ocular trauma. In the present trial the risk of PVR has been determined by laser flare photometry (objective tyndallometry). Previous studies confirmed that preoperative aqueous flare seems to be a major predictive factor for PVR re-detachment.[3,4]

Based on the results of the present study, we have reason to assume that the risk of the included patients was not increased. The total PVR rate was approximately 9% for Verum and for Placebo and is therefore comparable and not increased. One could conclude that the measurement using laser flare photometry does not determine the risk of PVR development, or that it is at least not the main factor. Perhaps there are other previously unknown risk factors for PVR. However, it appears, that it was not possible in our trial to identify the population at risk and therefore the overall PVR-rate in our study population remained below the previously assumed value of 35% for Placebo and 23% for Verum arm.

Furthermore, we cannot exclude, that the IMP might have been ineffective. Due to the overall low PVR rate, this would have been hardly assessable.

It would be desirable to address these questions in further clinical studies to identify the relevant risk factors for PVR development.

Altogether, we could not demonstrate a difference in incidence of PVR between treatment with intraoperative intravitreal 5-FU and LMWH and Placebo treatment.

References

1.Sundaram V, Barsam A, Virgili G. Intravitreal low molecular weight heparin and 5-Fluorouracil for the prevention of proliferative vitreoretinopathy following retinal reattachment surgery. Cochrane Database Syst Rev 2013; 1;CD006421.

2. Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 1999;55:1286-1290.

3. Schroder S, Muether PS, Caramoy A et al. Anterior chamber aqueous flare is a strong predictor for proliferative vitreoretinopathy in patients with rhegmatogenous retinal detachment. Retina 2012;32(1):38-42.

4. Conart JB, Kurun S, Ameloot F, Trechot F, Leroy B, Berrod JP. Validity of aqueous flare measurement in predicting proliferative vitreoretinopathy in patients with rhegmatogenous retinal detachment. Acta Ophthalmol 2016.

Figures

Figure 1: Trial sequence

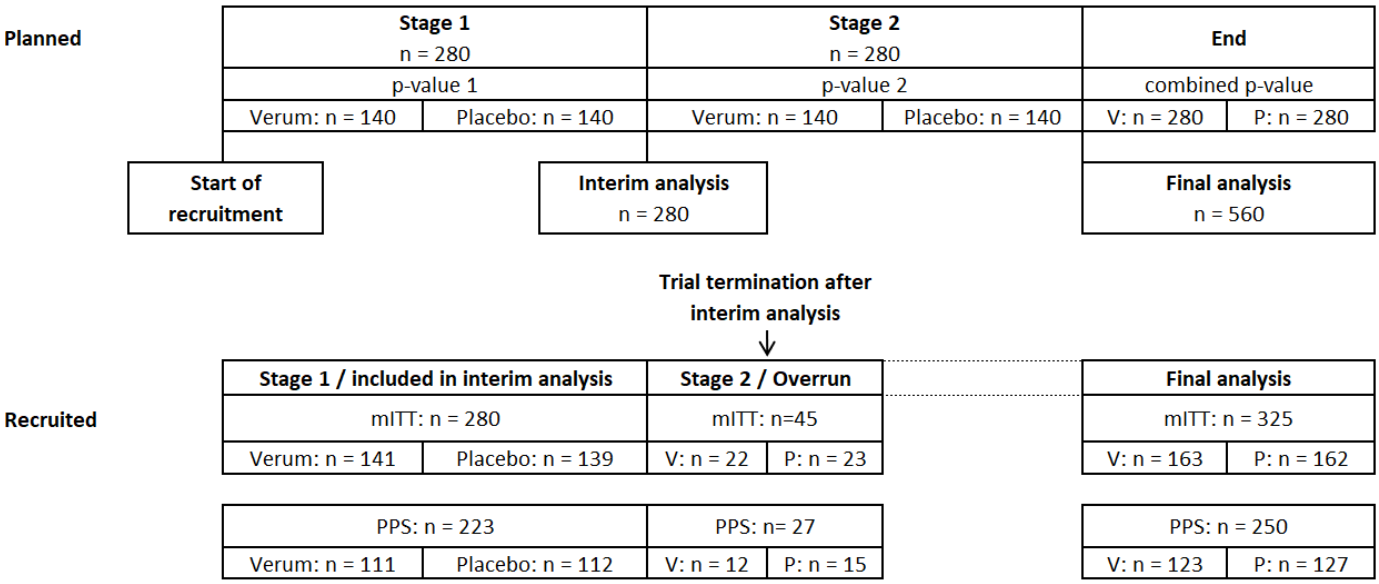
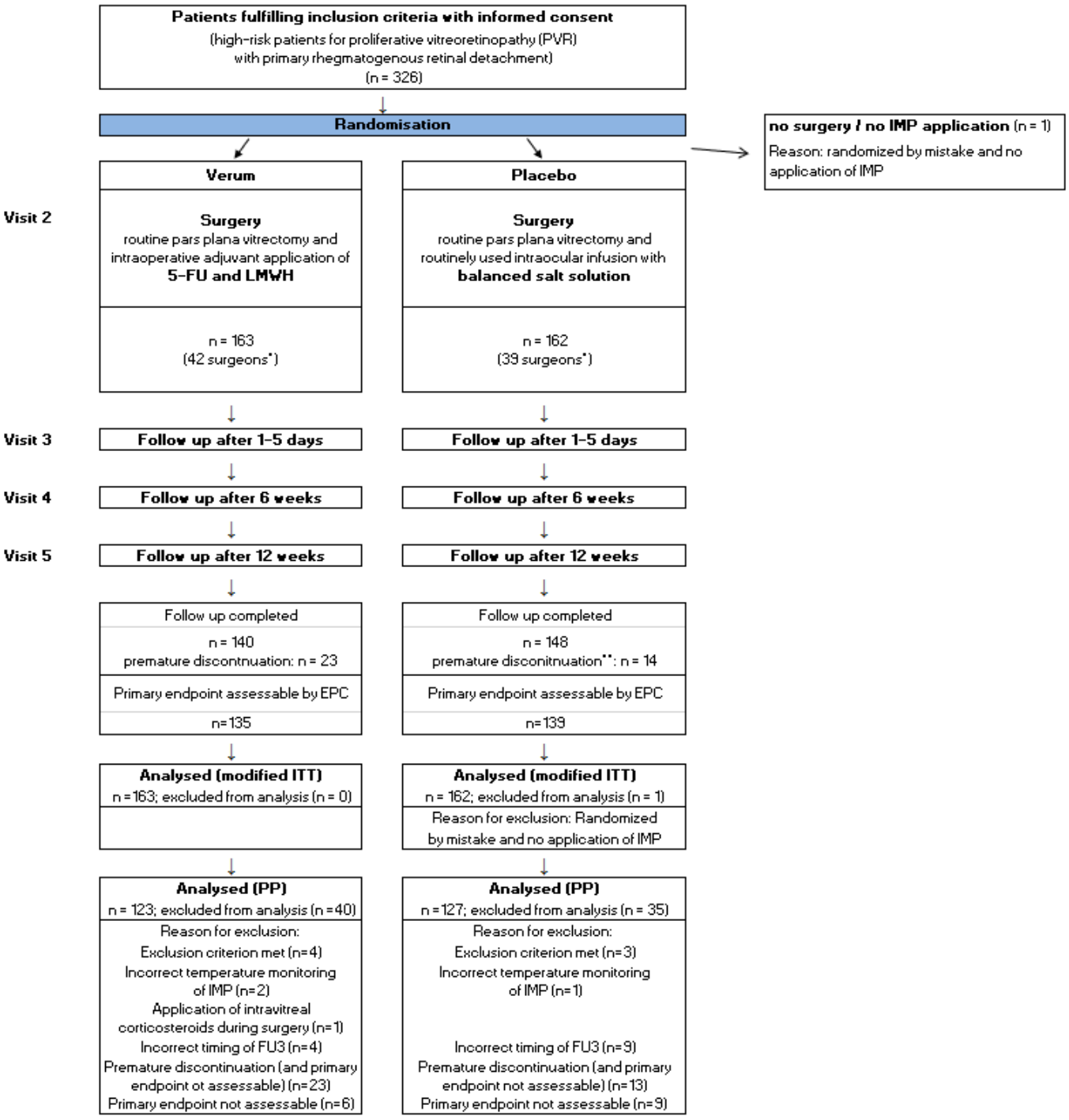


Figure 2: CONSORT Flow Diagram

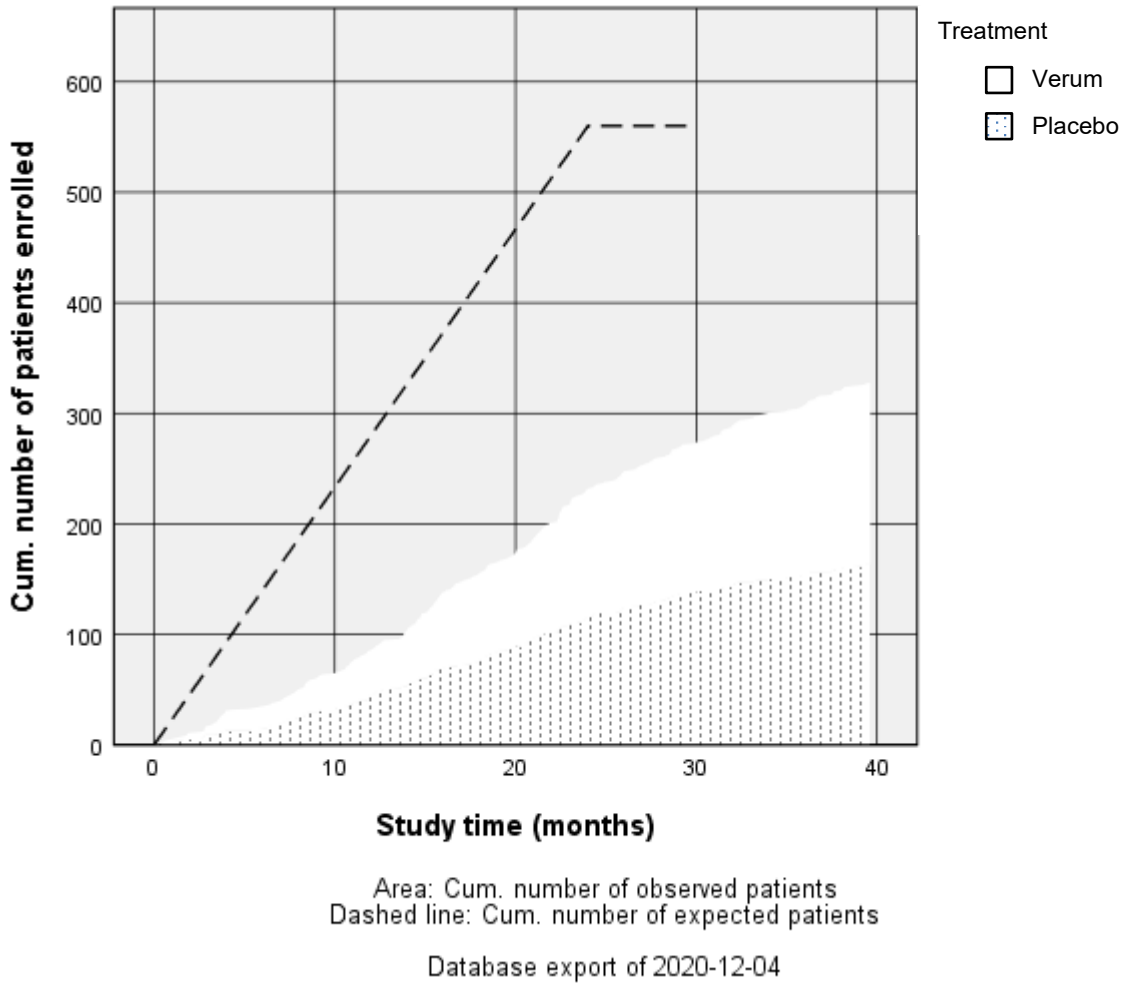


ITT = intention to treat; LMWH = low molecular weight heparin; 5-FU = 5-Fluorouracil; pc/ms = photon counts per milisecond; PP = per protocol)

*Number of surgeons who operated trial patients, per centre: 1 to 6; number of patients per centre: 1 to 48

** Number includes one patient who premature discontinued but which primary endpopint could be assessed by the EPC due to an early re-surgery

Figure 3: Recruitment



Tables

Table 1: Description of preoperative characteristics **(all patients, mITT)**

Characteristic		Total (n=325)	5-FU + Dalteparin (n=163)	Placebo (n=162)
Sex	Male, n (%)	242 (74)	124 (76)	118 (73)
	Female, n (%)	83 (26)	39 (24)	44 (27)
Age, years*	Mean (SD)	65 (10)	66 (9)	64 (10)
	Median (IQR)	64 (58 to 70)	65 (58 to 70)	63 (56 to 71)
Affected eye	Right, n (%)	175 (54)	90 (55)	85 (52)
	Left, n (%)	150 (46)	73 (45)	77 (48)
Average laser flare value (pc/ms)¥				(20)
Study eye	Mean (SD)	31 (26)	33 (30)	29
	Median (IQR)	23 (18 to 31)	24 (19 to 32)	22 (18 to 30)
Partner eye	Mean (SD)	11 (10)	11 (8)	12 (11)
	Median (IQR)	9 (6 to 13)	9 (6 to 13)	9 (6 to 13)
Lens status	Phakic	113 (35)	55 (34)	58 (36)
	Pseudophakic	212 (65)	108 (66)	104 (64)
Extend of retinal detachment (quadrants)	1	28 (9)	13 (8)	15 (9)
	2	146 (45)	74 (45)	72 (44)
	3	96 (30)	49 (30)	47 (29)
	4	55 (17)	27 (17)	28 (17)
Macula detached	No	104 (32)	53 (33)	51 (32)
	Yes	220 (68)	109 (67)	111 (68)
Spherical equivalent‡	Mean (SD)	-0.6 (3.4)	-0.7 (2.6)	-0.4 (4.0)
	Median (IQR)	0.0 (-1.9 to 0.5)	-0.2 (-2.3 to 0.4)	0.0 (-1.5 to 0.5)

Axis, degree‡	Mean (SD)	68 (58)	68 (57)	68 (59)
	Median (IQR)	70 (0 to 108)	70 (0 to 102)	70 (1 to 109)
Visual acuity (logMAR) §	Mean (SD)	1.0 (0.7)	0.9 (0.7)	1.0 (0.7)
	Median (IQR)	1.0 (0.3 to 1.8)	1.0 (0.3 to 1.8)	1.0 (0.3 to 1.8)
Cataract surgery	n (%)	207 (63)	105 (64)	102 (63)
	Uneventful, n (%)	205 (99)	105 (100)	100 (98)

Summary statistics are either count (percentage), mean (SD) or median (25th to 75th percentile), contingent on distributional characteristics.
*p = 0.073 and ¥p = 0.083 from Pearson's χ^2-test.
§Percentage of missing data ≤ 1.5 %, otherwise complete data.
‡Percentage of missing data 17 %

Table 2: Evaluation of primary outcome PVR grade CP1 or higher within 12 weeks after initial surgery

Primary endpoint (all patients): **PVR grade CP 1 or higher**	**5-FU + Dalteparin (V)**	**Placebo (P)**	**Odds ratio V vs P (95%-CI)**	**1-sided *P* value**
Modified intention-to-treat	**(n = 163)**	**(n = 162)**		
Primary analysis, stratified by surgeon				
No	118 (72)	124 (77)	1.25*	0.77§
Yes	45 (28)	38 (23)	(0.76 to 2.08)	
Final analysis (unbiased odds ratio and 95% CI)¥			1.71 (0.69 to 1.91)	0.70‡
Results of assessment by EPC				
No	118 (72)	124 (77)		
Yes	15 (9)	15 (9)		
Not assessable	30 (19)	23 (14)		
Reason for non-assessable PVR CP				
Due to poor quality	0 (0)	1 (<1)		
Photos not done	30 (19)	22 (14)		
thereof discontinued premature without FU3	23 (14)	13 (8)		
Per protocol	**(n=123)**	**(n=127)**		
Sensitivity analysis, stratified by surgeon				
No	108 (88)	112 (88)	1.05*	0.47§
Yes	15 (12)	15 (12)	(0.47 to 2.34)	
Final analysis (unbiased estimate and 95% CI)¥			0.90 (0.43 to 2.14)	0.46‡

Data are numbers (percentage), unless otherwise stated. (A non-assessable endpoint was counted as failure. Results separated by trial stage are given in the supplements 6h_Analysis_Primary_endpoint and 6h_PP_Analysis_Primary_endpoint.)

§Asymptotic *P* value (1-sided) from Cochran's Mantel-Haenszel test of conditional independence

**P* value (2-sided) from Breslow-Day test of homogeneity of odds ratios over surgeons, *P* = 0.39 (modified intention-to-treat) and *P* = 0.26 (per -protocol)

‡Adjusted *P* value (1-sided) based on the Tsiatis, Rosner and Mehta stagewise ordering [30]

¥95%-CI re-transformed from unbiased estimate and 95%-CI for standardized effect;

CI = confidence interval; EPC = endpoint committee; 5-FU = Fluorouracil; PVR = Proliferative Vitreoretinopathy; PVR grade CA: grade C anterior; PVR grade CP = grade C posterior. CP/CA, C = full-thickness retinal folds or subretinal strands in clock hours; P = located posterior to equator, A: located anterior to equator.

Table 3a: PVR grade CP or CA 1 or higher, 6 or 12 weeks after initial surgery (a non-assessable endpoint was counted as failure) and assessment results of EPC (mITT and PPS)

Secondary endpoint	**5-FU + Dalteparin (V)**	**Placebo (P)**
PVR grad CP 1 or higher (6 w)	**(n=163)**	**(n=162)**
Results of assessment by EPC		
No	130 (80)	134 (83)
Yes	6 (4)	6 (4)
Not assessable/no photos	27 (16)	22 (13)
PVR grad CA 1 or higher (6 w)	**(n=163)**	**(n=162)**
Results of assessment by EPC		
No	128 (78)	135 (83)
Yes	3 (2)	0 (0)
Not assessable/no photos	32 (20)	27 (17)
PVR grad CA 1 or higher (12 w)	**(n=163)**	**(n=162)**
No	124 (76)	129 (79)
Yes	39 (24)	33 (21)
Results of assessment by EPC		
No	124 (76)	129 (79)
Yes	3 (2)	1 (1)
Not assessable	36 (22)	32 (20)
Reason for non-assessable PVR CA (12 w)	**(n=36)**	**(n=32)**
Due to poor quality	5 (14)	5 (16)
Photo set incomplete	1 (3)	2 (6)
Photos not done	30 (83)	24 (75)
thereof discontinued without completing FU3	23 (64)	13 (41)
Re-surgeries due to re-detachment	**(n = 163)**	**(n=162)**
Patients with 1 re-surgery	19 (12)	25 (15)
Patients 2-3 re-surgeries	2 (12)	3 (2)
Retinal re-attachment after 12 weeks		
Achieved	12 (12/19=63%)	15 (15/25=60%)
Not achieved / not assessable	7 (7/19=37%)	10 (10/25=40%)

¥Due to the high proportion of cases not assessable, OR and p-value were not calculated fpr PVR grade CA;
EPC, endpoint committee, mITT, modified intention-to-treat set, OR, odds ratio, PPS, per-protocol set, PVR, proliferative Vitreoretinopathy, PVR grade CP, grade C posterior, PVR grade CA, grade C anterior
Note: Degree of PVR (CP 1-12 and CA 1-12) please see supplemental material, 6i_Analysis secondary endpoints, Table 1)

Table 3b: Evaluation of visual acuity in the course of the trial (mITT)

Endpoint	Group	Baseline	Week 6	Week 12	Difference W12 - baseline mean (95%-CI) *P*-value¥	Difference Verum - Placebo mean (95%-CI) *P*-value*
Visual acuity (logMAR)	Verum	0.9 ± 0.7 (n=160)	0.4 ± 0.5 (n=144)	0.3 ± 0.4 (n=134)	-0.55 (-0.65 to -0.44) < 0.001	0.03 (-0.05 to 0.11) 0.44
	Placebo	1.0 ± 0.7§ (n=161)	0.4±0.4 (n=147)	0.3 ± 0.3 (n=143)	-0.62 (-0.73 to -0.52) < 0.001	

Summary statistics are mean ± SD

¥ *P*-value derived from paired t-test (V: n = 132, P: n = 142)

* *P*-value derived from paired t-test (V: n=132, P: n=142); *P*-value derived from ANCOVA

CI = confidence interval; 5-FU = Fluorouracil; logMAR = logarithm of the Minimum Angle of Resolution

Table 3c: Further secondary endpoints

	Group	Week 6	Week 12	*P* value[a]
Retina fully attached after 12 weeks (assessed by EPC)	5-FU + Dalteparin	-	129 (99) (n = 130)	1.00
	Placebo	-	131 (98) (n = 133)	
Retinal re-attachment after primary surgery	5-FU + Dalteparin	124 (86) (n = 144)	116 (85) (n = 137)	0.63
	Placebo	119 (81) (n = 147)	116 (82) (n = 141)	
Occurrence of at least one drug-related adverse event with effect on the study eye within 12 weeks	5-FU + Dalteparin	-	10 (6) (n = 163)	0.82
	Placebo	-	11 (7) (n = 162)	

Data are numbers (percentage), unless otherwise stated.
[a] *P* value (2-sided) from Pearson's χ^2 test
5-FU = Fluorouracil

Table 4a: Number of (S)AEs (not) related to study eye (unit of observation: event); preferred term category by received treatment

Preferrred term (category)	Received treatment		
	Total	5-FU + Dalteparin	Placebo
SAE related to study eye			
Irritation of conjunctiva and/or cornea	2	1	1
Vitreo-retinal disorders	63	31	32
Choroidal haemorrhage	1	0	1
Intraocular pressure decompensation	6	2	4
Other eye disorder	1	0	1
Total	**73**	**34**	**39**
SAE not related to study eye			
Irritation of conjunctiva and/or cornea	1	1	0
Vitreo-retinal disorders	3	1	2
Intraocular pressure decompensation	2	2	0
No eye disorder	10	4	6
Total	**16**	**8**	**8**
All SAEs	**89**	**42**	**47**
AE related to study eye			
Reduced visual acuity	84	47	37
thereof AE of special interest (AESI)	1	1	0
Intraocular inflammation	215	104	111
Irritation of conjunctiva and/or cornea	407	205	202
Irritation of eyelid	67	34	33
Cataract and irritation of natural lens	63	29	34
Irritations of artifical intraocular lens	28	13	15
Vitreo-retinal disorders	118	59	59
Choroidal haemorrhage	3	3	0
Intraocular haemorrhage	36	15	21
Intraocular pressure decompensation	82	38	44
Other eye disorder	51	20	31
No eye disorder	27	15	12
Total	**1181**	**582**	**599**
AE not related to study eye			
Intraocular inflammation	5	2	3
Reduced visual acuity	3	3	0
Irritation of conjunctiva and/or cornea	18	10	8
Irritation of eyelid	3	2	1
Cataract and irritation of natural lens	5	1	4

Irritations of artifical intraocular lens	2	1	1
Vitreo-retinal disorders	9	4	5
Intraocular haemorrhage	1	0	1
Intraocular pressure decompensation	5	3	2
Reduced visual acuity	3	3	0
Other eye disorder	2	0	2
No eye disorder	134	62	72
Total	**187**	**88**	**99**
All AEs (not serious)	**1368**	**670**	**698**
Sum (S)AEs, related to study eye	1254	616	638
Sum (S)AEs, not related to study eye	203	96	107
All (S)AEs	**1457**	**712**	**745**

Note: Database export of 2020-12-04, MedDRA coding of 2020-12-04

Table 4b: Number of (S)AEs related to study eye and related to study medication (unit of observation: event); preferred term category by received treatment

Relatedness to study medication	Preferrred term (category)	Total	Received treatment 5-FU + Dalteparin	Placebo
SAE				
Possible	Vitreo-retinal disorders	1	1	0
AE				
Probable/likely	Cataract and irritation of natural lens	1	0	1
	Vitreo-retinal disorders	1	1	0
	Total	2	1	1
Possible	Intraocular inflammation	6	1	5
	Reduced visual acuity	1	1	0
	Irritation of conjunctiva and/or cornea	3	2	1
	Cataract and irritation of natural lens	2	2	0
	Vitreo-retinal disorders	2	1	1
	Choroidal haemorrhage	1	1	0
	Intraocular haemorrhage	1	1	0
	Intraocular pressure decompensation	5	2	3
	Total	21	11	10
Conditional / unclassified	Vitreo-retinal disorders	1	0	1
	Total	1	0	1
Unassessable/unclassifiabl	Irritation of conjunctiva and/or cornea	1	1	0
	Vitreo-retinal disorders	1	1	0
	No eye disorder	1	0	1
	Total	3	2	1
All (S)AEs related		**27**	**14**	**13**

Note: Database export of 2020-12-04, MedDRA coding of 2020-12-04

Table 4c: (S)AEs: relatedness to study procedure and outcome by received treatment

Outcome of SAE	Preferred term (category)	Total	Received treatment 5-FU + Dalteparin	Placebo
SAEs related to study procedure				
Not recovered/resolved	Vitreo-retinal disorders	1	0	1
	Total	1	0	1
Recovered/resolved with sequelae	Vitreo-retinal disorders	16	11	5
	Total	16	11	5
Recovering/resolving	Vitreo-retinal disorders	4	2	2
	Total	4	2	2
Recovered/resolved	Conjunctival irritation	1	1	0
	Intraocular pressure decompensation	3	1	2
	Lens extraction	1	0	1
	Vitreo-retinal disorders	17	7	10
	Total	22	9	13
SAEs related to study procedure	**Total**	**43**	**22**	**21**
SAEs not related to study procedure				
Fatal	Cardiac failure	1	1	0
	Total	1	1	0
Not recovered/resolved	Maculopathy	1	1	0
	Total	1	1	0
Recovered/resolved with sequelae	Acute myocardial infarction	1	0	1
	Cerebrovascular accident	1	0	1
	Cholecystitis	1	0	1
	Concussion	1	0	1
	Constipation	1	0	1

	Intraocular pressure test abnormal	1	0	1
	Retinal detachment	1	1	0
	Ulna fracture	1	1	0
	Total	8	2	6
Recovering/resolving	Herpes ophthalmic	1	1	0
	Intraocular pressure increased	1	1	0
	Retinal detachment	3	2	1
	Subretinal fluid	1	1	0
	Total	6	5	1
Recovered/resolved	Angina pectoris	1	1	0
	Choroidal haemorrhage	1	0	1
	Corneal erosion	1	0	1
	Intraocular pressure increased	3	2	1
	Pain in extremity	1	0	1
	Pneumonia	1	1	0
	Retinal cryoablation	1	1	0
	Retinal detachment	21	6	15
	Total	30	11	19
SAEs not related to study procedure	**Total**	**46**	**20**	**26**
SAEs				
Fatal		1	1	0
Not recovered/resolved		2	1	1
Recovered/resolved with sequelae		24	13	11
Recovering/resolving		10	7	3
Recovered/resolved		52	20	32
All SAEs		89	42	47

Outcome of AE	Preferred term (category)	Total	Received treatment 5-FU + Dalteparin	Placebo
AEs (not serious)				
Related to study procedure		1003	485	518
Not related to study procedure		365	185	180
Outcome of AEs				
Not yet resolved		387	170	217
Condition improving		36	17	19
Resolved with sequelae		18	14	4
Resolved without sequelae		896	452	444
Unknown		31	17	14
All AEs (not serious)		1368	670	698

Note: Database export of 2020-12-04, MedDRA coding of 2020-12-04

Table 4d: SAEs and AEs: relationship to study medication and outcome by received treatment (outcome of SAE corresponds to the (early) outcome at the time when seriousness ends, the underlying AE might last longer and outcome at the end of the follow up might be another)

Outcome of SAE	Preferred term (summarized)	Total	Received treatment 5-FU + Dalteparin	Placebo
SAEs: relationship to study medication				
Relationship possible				
Recovered / resolved	Vitreo-retinal disorders	2	1	1
	Total	2	1	1
Relationship unassessable / unclassifiable				
Recovering / resolving	Vitreo-retinal disorders	1	1	0
	Total	1	1	0
Relationship unlikely				
Recovered / resolved	Irritation of conjunctiva and/or cornea	2	1	1
	Vitreo-retinal disorders	37	13	24
	Choroidal haemorrhage	1	0	1
	Intraocular pressure decompensation	6	3	3
	Other eye disorder	1	0	1
	No eye disorder	3	2	1
	Total	50	19	31
Recovering / resolving	Irritation of conjunctiva and/or cornea	1	1	0
	Vitreo-retinal disorders	7	4	3
	Intraocular pressure decompensation	1	1	0
	Total	9	6	3
Recovered / resolved with sequelae	Vitreo-retinal disorders	17	12	5
	Intraocular pressure decompensation	1	0	1
	No eye disorder	6	1	5
	Total	24	13	11

Not recovered / resolved	Vitreo-retinal disorders	2	1	1
	Total	2	1	1
Fatal	No eye disorder (heart failure)	1	1	0
	Total	1	1	0
All SAEs				
SAEs possibly related		3	2	1
SAEs not related		86	40	46
Recovered / resolved		52	20	32
Recovering / resolving		10	7	3
Recovered / resolved with sequelae		24	13	11
Not recovered / resolved		2	1	1
Fatal		1	1	0
All		89	42	47

			Received treatment	
Outcome of AE	**Preferred term (summarized)**	**Total**	**5-FU + Dalteparin**	**Placebo**
AEs: relationship to study medication				
Probable / likely				
Resolved without sequelae	Vitreo-retinal disorders	1	1	0
	Total	1	1	0
Not yet resolved	Cataract and irritation of natural lens	1	0	1
	Total	1	0	1
Possible				
Resolved without sequelae	Intraocular inflammation	1	0	1
	Cataract and irritation of natural lens	2	2	0
	Vitreo-retinal disorders	2	1	1
	Choroidal haemorrhage	1	1	0

	Intraocular pressure decompensation	5	2	3
	No eye disorder	2	0	2
	Total	13	6	7
Condition improving	Intraocular inflammation	1	0	1
	Irritation of conjunctiva and/or cornea	2	2	0
	Total	3	2	1
Not yet resolved	Intraocular inflammation	3	1	2
	Reduced visual acuity	1	1	0
	Irritation of conjunctiva and/or cornea	1	0	1
	Total	5	2	3
Unknown	Intraocular inflammation	1	0	1
	Intraocular haemorrhage	1	1	0
	No eye disorder	1	1	0
	Total	3	2	1
Relationship conditional / unclassified				
Not yet resolved	Vitreo-retinal disorders	1	0	1
	Total	1	0	1
Relationship unassessable / unclassifiable				
Resolved without sequelae	Cataract and irritation of natural lens	1	0	1
	Vitreo-retinal disorders	1	1	0
	Total	2	1	1
Not yet resolved	Irritation of conjunctiva and/or cornea	1	1	0
	No eye disorder	1	0	1
	Total	2	1	1
Relationship unlikely				
Resolved without sequelae	Intraocular inflammation	172	90	82
	Reduced visual acuity	63	33	30
	Other eye disorder	34	12	22
	Irritation of conjunctiva and/or cornea	310	166	144

	Irritation of eyelid	49	25	24
	Cataract and irritation of natural lens	16	8	8
	Irritations of artifical intraocular lens	15	6	9
	Vitreo-retinal disorders	37	18	19
	Choroidal haemorrhage	2	2	0
	Intraocular haemorrhage	29	12	17
	Intraocular pressure decompensation	66	28	38
	No eye disorder	87	44	43
	Total	880	444	436
Resolved with sequelae	Reduced visual acuity	4	4	0
	Other eye disorder	1	1	0
	Irritation of conjunctiva and/or cornea	3	1	2
	Irritation of eyelid	1	0	1
	Cataract and irritation of natural lens	1	1	0
	Vitreo-retinal disorders	3	2	1
	Intraocular pressure decompensation	3	3	0
	No eye disorder	2	2	0
	Total	18	14	4
Condition improving	Intraocular inflammation	5	3	2
	Reduced visual acuity	1	1	0
	Other eye disorder	1	1	0
	Irritation of conjunctiva and/or cornea	15	4	11
	Irritation of eyelid	2	0	2
	Vitreo-retinal disorders	5	2	3
	Intraocular pressure decompensation	2	2	0
	No eye disorder	2	2	0
	Total	33	15	18
Not yet resolved	Intraocular inflammation	34	11	23
	Reduced visual acuity	18	11	7

	Other eye disorder	15	5	10
	Irritation of conjunctiva and/or cornea	83	36	47
	Irritation of eyelid	16	10	6
	Cataract and irritation of natural lens	47	19	28
	Irritations of artifical intraocular lens	14	7	7
	Vitreo-retinal disorders	74	36	38
	Intraocular haemorrhage	7	2	5
	Intraocular pressure decompensation	11	6	5
	No eye disorder	59	24	35
	Total	378	167	211
Unknown	Intraocular inflammation	3	1	2
	Other eye disorder	2	1	1
	Irritation of conjunctiva and/or cornea	10	5	5
	Irritation of eyelid	2	1	1
	Irritations of artifical intraocular lens	1	1	0
	Vitreo-retinal disorders	3	2	1
	No eye disorder	7	4	3
	Total	28	15	13
All AEs (not serious)				
AEs possibly related		31	15	16
AEs not related		1337	655	682
Resolved without sequelae		896	452	444
Resolved with sequelae		18	14	4
Condition improving		36	17	19
Not yet resolved		387	170	217
Unknown		31	17	14
All AEs		1368	670	698

Note: Database export of 2020-12-04, MedDRA coding of 2020-12-04

Appendices

List of further analyses, i.e. PP-set, subgroups (list of further appendices -> PDFs)

1. 6a_Demography
2. 6a_female_demography
3. 6a_male_demograph
4. 6a_PP_demography
5. 6a_PP_female_demography
6. 6a_PP_male_demography
7. 6b_Analysis_sets
8. 6c_Analysis_Medical_history
9. 6c_female_Analysis_Medical_history
10. 6c_male_Analysis_Medical_history
11. 6d_Analysis_Exposition_to_treatment
12. 6e_Co-medication
13. 6f_Adverse_events
14. 6g_Analysis_Complications
15. 6h_Analysis_Primary_endpoint
16. 6h_female_Analysis_Primary_endpoint
17. 6h_male_Analysis_Primary_endpoint
18. 6h_PP_Analysis_Primary_endpoint
19. 6h_PP_female_Analysis_Primary_endpoint
20. 6h_PP_male_Analysis_Primary_endpoint
21. 6i_Analysis_Secondary_endpoints
22. 6i_female_Analysis_Secondary_endpoints
23. 6i_male_Analysis_Secondary_endpoints
24. 6i_PP_Analysis_Secondary_endpoints
25. 6i_PP_female_Analysis_Secondary_endpoints
26. 6i_PP_male_Analysis_Secondary_endpoints
27. 6j_Analysis_Re-surgeries
28. 6k_Analysis_Ophthalmological_examination
29. 6l_Analysis_Laboratory_tests