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Study ID: 206207-026

Title: Dexamethasone Posterior Segment Drug Delivery System Versus Laser Photocoagulation in Patients With Diabetic Macular Edema

Protocol Amendment 1 Date: 25Apr2013

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STUDY TITLE

Dexamethasone Posterior Segment Drug Delivery System Versus Laser Photocoagulation in Patients with Diabetic Macular Edema

Protocol Number:	206207-026
Phase:	3
Name of Investigational Product:	Dexamethasone Posterior Segment Drug Delivery System
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612
Emergency Telephone Number: Serious Adverse Event Reporting Fax Numbers: Allergan Medical Safety Physician Contact Information: Allergan Signatory:	[redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

STUDY LOCATION:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

RETURN TO ALLERGAN WITH ATTACHED PROTOCOL

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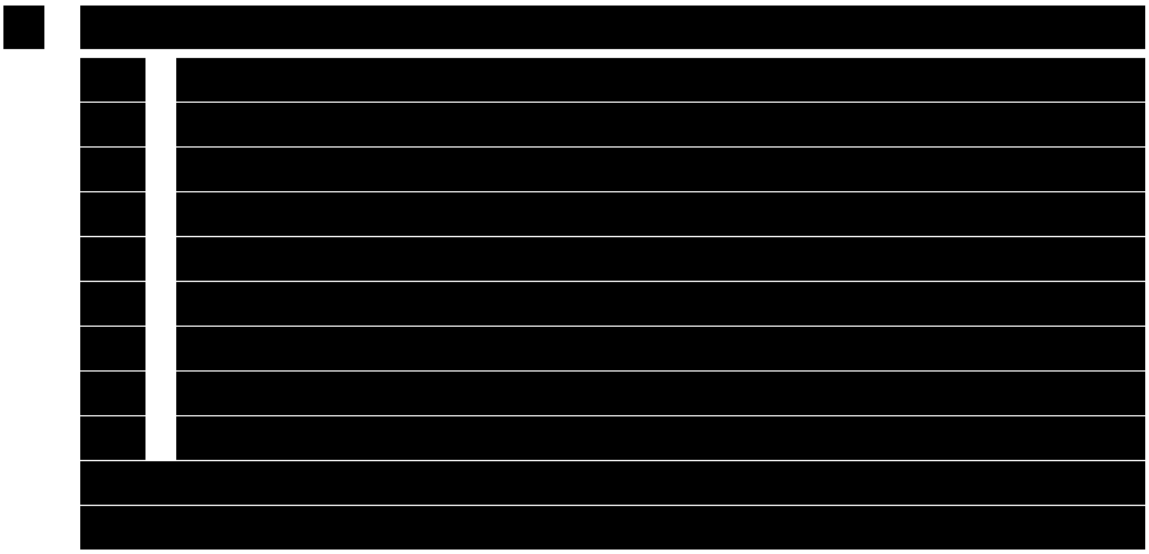

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Protocol Summary

Study Compound: 700 µg dexamethasone posterior segment drug delivery system (DEX PS DDS)

Phase: 3

Study Objectives:

- To evaluate the safety and efficacy of the 700 µg DEX PS DDS compared with laser photocoagulation in patients with diabetic macular edema (DME)

Clinical Hypotheses:

- Treatment with 700 µg DEX PS DDS every 5 months is superior to laser photocoagulation according to the modified Early Treatment Diabetic Retinopathy Study (ETDRS) protocol with respect to the average change from baseline of best-corrected visual acuity (BCVA) during 12 months of treatment for DME
- 700 µg DEX PS DDS administered every 5 months has an acceptable safety profile

Study Design:

Structure: multicenter, randomized, comparative study

Duration: 12 months

Study Treatment Group: 700 µg DEX PS DDS

Control: laser photocoagulation according to the modified ETDRS protocol

Dosage/Dose Regimen:

- 700 µg DEX PS DDS every 5 months
- Laser photocoagulation as needed according to ETDRS protocol every 3 months if
    - Optical coherence tomography (OCT) central subfield ≥ 250 µm with Stratus III (Zeiss), ≥ 275 µm with Cirrus (Zeiss) or ≥ 300 µm with Spectralis (Heidelberg)

  AND
    - Patient might benefit from retreatment in the opinion of the investigator

Randomization/Stratification: 1:1 randomization, stratification by BCVA score (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) at baseline within each study site

[redacted]

Study Population Characteristics:

Number of Patients: Approximately 356 patients will be enrolled at 20 sites to ensure that at least 151 patients in each treatment group complete the study.

Condition/Disease: DME

Key Inclusion Criteria:

- male or female, at least 18 years of age
- prior diagnosis of diabetes mellitus (type 1 or type 2)
- presence of macular edema associated with diabetic retinopathy, defined as macular thickening by OCT as assessed by the investigator in the study eye involving the center of the macula (fovea) and with visual acuity (VA) decrease attributable to macular edema

[redacted]

Key Exclusion Criteria:

[redacted]

- laser photocoagulation to the retina of the study eye within 3 months prior to screening

[redacted]

Response Measures

Efficacy: BCVA measured by ETDRS, central retinal thickness measured by OCT, area of macular leakage measured with fluorescein angiography (FA)

[redacted]

General Statistical Methods and Types of Analyses:

Analysis Populations: Three populations will be used for statistical analyses: modified intent-to-treat (mITT), per-protocol (PP), and safety.

Primary Efficacy Analysis: The primary efficacy endpoint is the average change from baseline in BCVA over 12 months. The primary analysis will be an analysis of covariance (ANCOVA) comparing the treatment difference in the mean average BCVA change from baseline in a 12-month study period. The ANCOVA model will include the treatment group as the main effect and baseline BCVA score as the covariate. The average change will be computed by subtracting the baseline BCVA from the area under the BCVA curve (AUC) divided by the total follow-up time for each patient. Calculations for AUC will be based on observed data using

the trapezoidal method and will include all postbaseline BCVA data for the patient from the study treatment to the last VA measurement, regardless of scheduled or unscheduled visits.

Secondary Efficacy Analyses: Secondary efficacy analyses include a Cochran–Mantel-Haenszel (CMH) test stratified within each study site by baseline BCVA categories (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) for treatment difference in proportion of patients with ≥ 15 letters improvement from baseline of BCVA at month 12; and ANCOVA on retinal thickness and total leakage area at month 12.

[redacted]

[redacted]

1. Background and Clinical Rationale

Diabetes affects more than 220 million people worldwide (World Health Organization, WHO Diabetes Fact Sheet, 2011) and its prevalence is expected to grow to 366 million by 2030 (Wild et al, 2004). Diabetic macular edema (DME) is 1 of the major causes of vision loss in patients with diabetic retinopathy (Resnikoff et al, 2004). Diabetic retinopathy (DR) and DME are common microvascular complications in patients with diabetes and may have sudden and debilitating impact on VA, eventually leading to blindness. DME is a frequent manifestation of DR and is a major cause of vision loss in patients with DR. DME results from retinal microvascular changes. Thickening of the basement membrane and reduction in the number of pericytes are believed to lead to increased permeability and incompetence of the retinal vasculature. This compromise of the blood-retinal barrier (BRB) leads to the leakage of plasma constituents into the surrounding retina, with subsequent retinal edema (Albert and Jakobiec, 2000). Increase of vascular permeability and breakdown of the BRB in DME is thought to be caused by vascular epithelial growth factor (VEGF) effects, such as phosphorylation of tight junctional protein occludin and Fas-mediated endothelial cell apoptosis, and also by inflammatory effects like leukostasis, possibly due to increased expression of leukocyte adhesion molecules (Aiello et al, 1997).

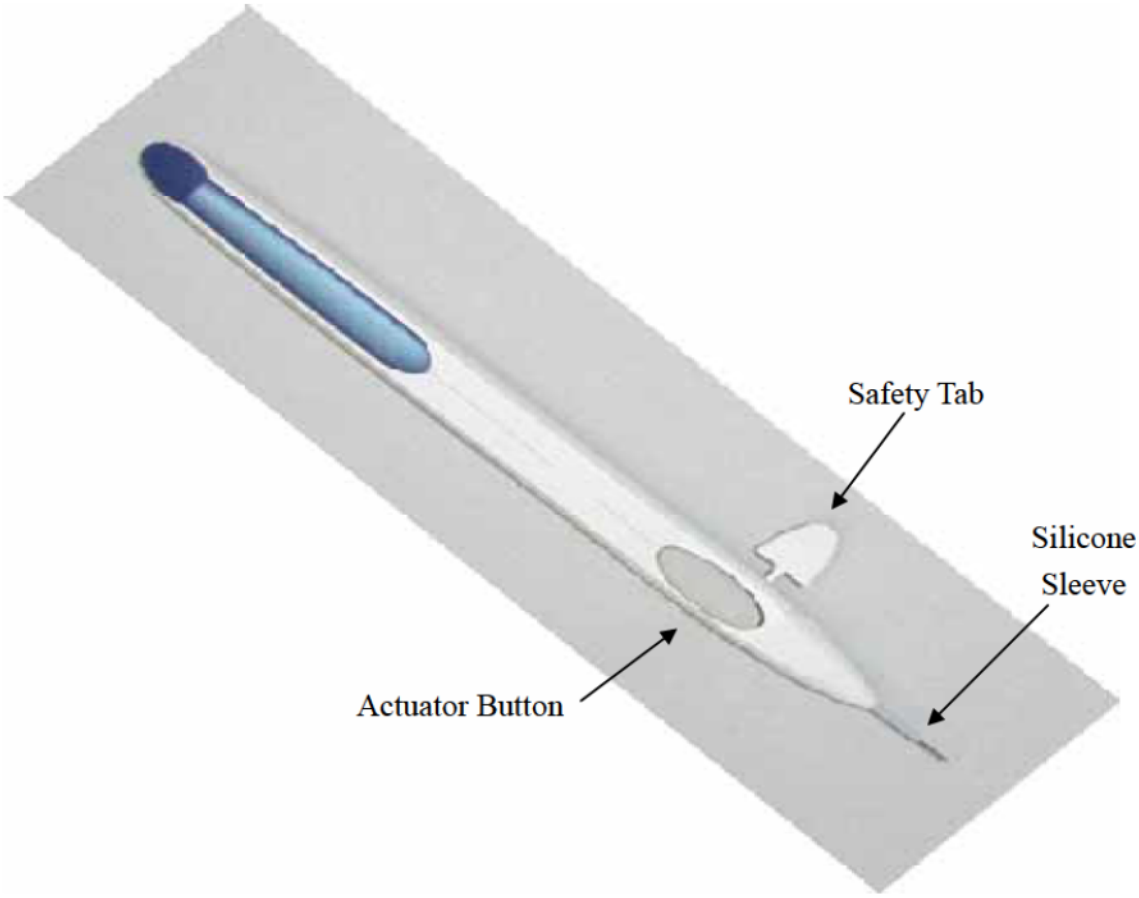
Laser photocoagulation has been shown to be efficacious in the prevention of mild to moderate vision loss from DME (ETDRS Report #1, 1985). In the ETDRS protocol, laser photocoagulation reduced the risk of moderate visual loss from DME by 50% (from 24% to 12% 3 years after initiation of treatment (ETDRS Report #2, 1987). However, few patients experience improvement in vision following laser alone for DME, and persistent and recurrent macular edema is common (ETDRS Report #9, 1991). DME due to DR may come from discrete points of leakage (focal edema) or from geographic areas of diffuse retinal vascular hyperpermeability (diffuse edema). Diffuse diabetic macular edema is particularly refractory to laser treatment (Bresnick, 1983). The present study will use a modified EDTRS protocol (Modified-ETDRS Focal Photocoagulation Technique [Internet], 2006) commonly used in clinical practice (See Section 12.1.11).

Ranibizumab has been approved for the treatment of DME in Europe and more recently (August 2012) in the USA. However, in China, for example, ranibizumab is approved only for treatment of age-related macular degeneration (AMD) and laser photocoagulation remains the current standard of care for DME.

Corticosteroids modulate vascular permeability through anti-inflammatory effects, in addition to suppressing production of VEGF and other permeability factors.

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting edema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. In the past, the use of dexamethasone has yielded limited success in treating retinal disorders including macular edema, largely due to the inability to deliver and maintain adequate quantities of the drug to the posterior segment (Ahmed and Ai, 1999). The dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) delivers a 700 µg total dose of dexamethasone to the vitreous with gradual release over time (Investigators Brochure) allowing for sustained drug levels to the target areas. DEX PS DDS is composed of dexamethasone homogeneously dispersed into a biodegradable matrix composed of copolymers of lactic acid and glycolic acid, PLGA (poly [lactic-glycolic] acid), a material commonly used in medical devices such as absorbable sutures (Moritera et al, 1991; Singhal et al, 1988; Vicryl® package insert, 1997; Visscher et al, 1985). The DEX PS DDS does not need to be removed since the copolymer dissolves and absorbs over time. An applicator (see Figure 2) was designed to facilitate intravitreal placement of the extruded DEX PS DDS. By effectively delivering dexamethasone into the vitreous, DEX PS DDS offers a valuable new therapeutic option in the treatment of macular edema.

Figure 2 **Dexamethasone Posterior Segment Drug Delivery System**



Two large, double-masked, well-controlled phase 3 clinical studies evaluated the safety and efficacy of the 700 µg DEX PS DDS Applicator System (Figure 2) in 1267 patients with macular edema associated with retinal vein occlusion (RVO) (Clinical study reports 206207-008, 6-month and 206207-009, 6-month). Findings from the phase 3 studies demonstrated statistically significant efficacy of the 700 µg DEX PS DDS compared to sham control as measured by the time to achieve a treatment response of 15 or more letters improvement in BCVA from baseline. The cumulative response rate was consistently higher with DEX PS DDS treatment compared to SHAM control throughout the 6-month treatment period. In addition, DEX PS DDS-treated patients achieved their treatment response much earlier than sham patients (starting from day 30, and further separating at day 60), which provides greater potential for visual recovery. The 700 µg DEX PS DDS was well tolerated, with less than 2% of patients in the phase 3 studies discontinuing due to adverse effects. An acceptable safety profile for dexamethasone in the drug delivery applicator system was demonstrated.

One of the most frequently reported adverse events associated with ophthalmic corticosteroid use is elevated intraocular pressure (IOP). Although elevations of IOP were significantly more prevalent with DEX PS DDS than with sham, the increases either did not require treatment or were managed with topical IOP-lowering medications. Like all injectable steroids, there was a higher incidence of cataracts with DEX PS DDS (7.4%) compared to sham (4.5%). However, only 2 cataract surgeries were performed in the study eye (SE) during the 6-month study period.

In the pivotal studies for patients with macular edema secondary to RVO, 98% of patients received a second injection of DEX PS DDS between 5 and 7 months after the initial treatment. Post hoc analysis of these previous studies suggest that patients dosed between months 5 and 6 have better outcomes than the overall study population.

Allergan has completed 1 phase 2 study with 700 µg DEX PS DDS in patients with DME. Study 206207-012 (PLACID study) was a 52-week, masked, multicenter, randomized, controlled trial (with up to 13 weeks additional follow up) to assess the safety and efficacy of 700 µg DEX PS DDS in combination with laser photocoagulation in the treatment of patients with diffuse DME. A total of 253 patients were randomized and enrolled in the study: 126 in the Combination Therapy group and 127 in the Laser Alone group. Intravitreal injection with 700 µg DEX PS DDS in combination with laser treatment was shown to provide more prolonged reduction in macular thickening and better VA overall than laser alone in patients with diffuse DME. Treatment with combination therapy led to better outcomes than laser alone in improving vision at month 1 (31.7% versus 11.0%; $p < 0.001$) and at month 4 (26.2% versus 16.5%; $p = 0.060$) in the ITT population. There was no statistically significant difference between the treatment groups at month 6.

The aim of this study is to demonstrate that DEX PS DDS administered every 5 months will lead to greater improvement of VA than laser photocoagulation over 1 year of treatment.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objective

The objective of this study is to evaluate the safety and efficacy of the 700 µg DEX PS DDS compared with laser photocoagulation in patients with DME.

2.2 Clinical Hypotheses

- Treatment with 700 µg DEX PS DDS every 5 months is superior to laser photocoagulation according to the modified ETDRS protocol (with respect to the average change from baseline of BCVA during 12 months of treatment for DME)
- 700 µg DEX PS DDS administered every 5 months has an acceptable safety profile

3. Study Design

This study is a multicenter, randomized, 12-month comparative study to evaluate if 700 µg DEX PS DDS administered every 5 months is safe and can achieve improvement of BCVA superior to laser photocoagulation administered according to the modified ETDRS protocol (Section 12.1.11).

Consenting patients will participate in a screening period lasting 2 to 14 days to evaluate patient eligibility. After eligibility has been determined by the investigator, patients will be randomized in a 1:1 ratio to receive:

- 700 µg DEX PS DDS every 5 months
  or
- laser photocoagulation according to the modified ETDRS protocol

The randomization will be stratified by BCVA score at baseline (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) within each investigator site. The primary efficacy measure is average change of BCVA over a period of 12 months. The total duration of study participation for each patient is approximately 12.5 months including screening and randomization/retreatment period. Patients will attend the following 11 visits: screening visit, randomization visit, 8 assessment/retreatment visits, and study exit visit.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 356 patients will be enrolled at approximately 20 sites to ensure that at least 151 patients in each treatment group complete the study. Of those, approximate10 patients assigned to DEX PS DDS at selected sites will participate in therapeutic drug monitoring.

4.2 Study Population Characteristics

Patients with DME in at least 1 eye will be enrolled. If both eyes are eligible for the study, the eligible eye with worse VA should be selected as the SE. The SE will be identified at the Screening visit and confirmed at the randomization visit and will remain the same throughout the entire study duration.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. male or female, at least 18 years of age
2. prior diagnosis of diabetes mellitus (type 1 or type 2)
3. presence of macular edema [redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

Systemic conditions or treatments:

[redacted]

10. anticipated need for ocular surgery in the SE during the 1-year study participation

[redacted]

13. laser photocoagulation to the retina of the SE within 3 months prior to screening

[redacted]

18. history of cataract surgery within the 3 months prior to screening

[redacted]

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patients' welfare may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, these medications should be administered in dosages that remain constant throughout the course of the trial. If the permissibility of a specific medication or treatment is in question, please contact Allergan.

Treatment of elevated IOP: The need for treatment for elevated IOP will be at the discretion of the investigator. Consultation with glaucoma specialists should be considered when necessary.

Cataract surgery: If a patient develops visually significant cataracts during the study period, the decision to perform cataract surgery is left to the discretion of the investigator and the patient. Cataract surgery should be considered under the following conditions:

- visual function no longer meets the patient's needs and cataract surgery provides a reasonable likelihood of improvement
- lens opacity inhibits optimal management of posterior segment disease
- the lens causes inflammation (phacolysis, phacoanaphylaxis), angle closure, or medically unmanageable open-angle glaucoma

Topical steroids, periocular, or intravitreal steroid injections: allowed to treat inflammatory conditions in **nonstudy eye**

Intravitreal anti-VEGF treatment: allowed in the **nonstudy eye**

Use of systemic nonsteroidal anti-inflammatory drugs (NSAIDs): systemic NSAIDs regularly used prior to enrollment will be allowed to continue during the study, and should be administered at a dosage that remains constant throughtout the course of the trial.

Nonocular steroids: low-dose creams and ointments; intraarticular, inhaled, intranasal and ear drops allowed

Panretinal photocoagulation: if needed to treat neovascularization

For patients who are assigned to DEX PS DDS drug monitoring, no corticosteroids (except the study medication) are allowed during the first 6 months.

4.5.2 Acceptable Contraceptive Methods

Women of childbearing potential must use reliable contraception. The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

If a female of childbearing potential becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed, and the patient will be exited from the study after appropriate safety follow up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug (if applicable), 700 µg DEX PS DDS, and (2) follow the progress of the pregnancy. The investigator should discontinue study treatment, document the outcome of the pregnancy, and provide a copy of the documentation to Allergan.

4.5.3 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

The following medications should be avoided during the study:

- SE-intravitreal injections of any sort other than the study medication
- SE-sub-tenon, subconjunctival or topical corticosteroids

- systemic corticosteroids (oral, inhaled, intranasal, intravenous, intramuscular, epidural, rectal, or extensive dermal); for patients who are assigned to DEX PS DDS drug monitoring any form of dexamethasone should be avoided during the first 6 months.
- systemic anti-VEGF therapies
- systemic immunosuppressants, immunomodulators, antimetabolites or alkylating agents
- systemic carbonic anhydrase inhibitors (eg Diamox)
- SE-additional invasive nonstudy procedures or surgery

If the permissibility of a specific medication/treatment is in question, please contact Allergan.

5. Study Treatments

5.1 Study Treatments and Formulations

The study treatment will be dexamethasone intravitreal implant containing 700 µg dexamethasone in a solid polymer delivery system.

5.2 Control Treatment

The control treatment will be laser photocoagulation according to modified ETDRS protocol.

5.3 Escape Therapy

Treatment according to standard of care (SOC) should be considered for patients with a decrease of BCVA > 10 ETDRS letters from baseline, which is confirmed at 2 consecutive visits. Patients who receive escape therapy will no longer eligible to receive study treatment, but will continue in the study for safety assessments.

5.4 Methods for Masking/Blinding

Study personnel collecting primary efficacy (BCVA) data and evaluators at the reading center will be blinded to study treatment assignment for the duration of the trial. The BCVA technician may not assist nor be present during the treatment procedure, as they need to remain unaware of patient treatment assignments.

5.5 Treatment Allocation Ratio and Stratification

Patients will be randomized in a 1:1 ratio to either 700 µg DEX PS DDS or laser photocoagulation.

The randomization will be stratified by BCVA score at baseline (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) within each study site.

5.6 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study treatment, each patient who provides informed consent and/or assent will be assigned a patient number that will serve as the patient identification number on all study documents.

An automated interactive voice response system (IVRS) or interactive web response system (IWRS) will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan Biostatistics.

Study medication will be labeled with medication kit numbers. The IVRS/IWRS system will provide the site with the specific medication kit number(s) for each randomized subject at the time of randomization. Sites will dispense study medication/treatment according to the IVRS/IWRS instructions. Sites will also call the IVRS or log onto the IWRS at subsequent visits to obtain a study medication kit number for dispensing study medication. Sites will receive the IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

5.7 Treatment Regimen and Dosing

5.7.1 DEX PS DDS

Patients assigned to the DEX PS DDS treatment group will receive 700 µg dexamethasone in a solid polymer delivery system at day 1, months 5, and 10.

5.7.2 Laser Photocoagulation

Patients assigned to the laser photocoagulation treatment group will receive laser treatment on day 1.

Repeat laser photocoagulation at months 3, 6, and 9 will be administered if both of the following conditions are met:

- OCT central subfield ≥ 250 µm with Stratus III (Zeiss), ≥ 275 with Cirrus (Zeiss) or ≥ 300 µm with Spectralis (Heidelberg)
- patient might benefit from retreatment in the opinion of the investigator

Laser treatment will be given according to the modified ETDRS treatment protocol (Section 12.1.11).

5.8 Storage of Study Medication

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

DEX PS DDS: [redacted]

5.9 Study Drug Administration

5.9.1 Peri-operative Anti-infective Treatment

At the visit preceding each study drug administration, the patient will be given antibiotic ophthalmic solution (as applicable according to local practice) and instructed to instill a drop in the SE 4 times per day (QID) for 3 days prior to the study treatment procedure and up to QID (depending on the time of the study treatment procedure) on the day of the procedure, and QID for 3 days postoperatively. Patients should be instructed not to wear contact lenses while using antibiotics. See the Procedure Manual for further details.

5.9.2 Product Dispensing

Only qualified patients will receive study treatment. The assigned staff member will access the IVRS/IWRS after patient randomization has been completed approximately 30 minutes

prior to the study treatment procedure to receive study treatment kit numbers that can be used for each patient (see the Procedure Manual for the IVRS/IWRS details). Upon initial access to the IVRS/IWRS, a study treatment kit will be dispensed. In the unlikely event that the initial applicator fails, the assigned staff member will access the IVRS/IWRS again to receive a second study treatment kit number to use. Although it is not expected that further kits will be required, should further study treatment kits fail, up to a fourth kit may be obtained by accessing the IVRS/IWRS again. If the fourth study treatment kit fails, the study treatment procedure should be aborted, and Allergan should be notified immediately.

The DEX PS DDS must only be handled at the time of the procedure and only under sterile conditions. The study medication must be placed in enrolled patients' eyes by an investigator who possesses acceptable experience as determined by Allergan.

5.9.3 Final Product Disposition

The used applicators will be destroyed by the site. For unused malfunctioning applicators, the assigned site personnel will record the nature of the malfunction on the appropriate form. The malfunctioning applicators will be destroyed by the site. All unused applicators will be returned for destruction according to Allergan instructions.

5.9.4 Operative Procedure

The study treatment procedure must be performed only in an operating room, surgical suite, or in an office setting using a sterile technique, as described in the Procedure Manual. The study treatment kit(s) should be readily available during the procedure.

Prior to study treatment, the SE of each patient will be anesthetized with topical and/or subconjunctival anesthetic and prepared according to the investigator's standard of practice. Patients randomized to active treatment will have the study drug placed into the vitreous through the pars plana using the DEX PS DDS. See the Procedure Manual for further details.

Once the DEX PS DDS is deployed, the lever becomes locked to indicate that the applicator has been used and prevents reuse.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

The primary efficacy measure will be BCVA measured by ETDRS.

6.1.2 Secondary Efficacy Measures

Secondary efficacy measures will be:

- central retinal thickness measured by OCT
- total area of macular leakage measured on FA

[redacted]

6.4 Examination Procedures, Tests, Equipment, and Techniques

6.4.1 Best-corrected Visual Acuity

BCVA in the SE and in the nonstudy eye will be measured using the ETDRS VA protocol following manifest refraction. All BCVA data will be used to assess safety as well as efficacy.

6.4.2 Optical Coherence Tomography

OCT is a laser-based, noninvasive, diagnostic system providing high-resolution imaging optical sections of the retina. The mean retinal thickness in the 1-mm central subfield of the SE will be captured using time-domain OCT (Stratus III, Zeiss) or spectral-domain OCT (Cirrus, Zeiss or Spectralis, Heidelberg). Electronic OCT images will be collected for evaluation by a reading center. Once an OCT instrument has been selected for a patient, that instrument must be used for all the study assessments for that patient for the duration of the study.

6.4.3 Fluorescein Angiography

Early and transit images will be taken of the SE. Mid- and late-phase images will be taken of the study and nonstudy eye. Electronic FA images will be collected for evaluation by a reading center.

6.4.4 Intraocular Pressure Measurement

IOP will be measured using a Goldmann applanation tonometer instrument or a hand held tonometer. Once an instrument for IOP measurement has been selected for a patient, that instrument must be used for all the study assessments for that patient for the duration of the study.

6.5 Other Study Supplies

Laboratory kits for the collection and shipment of hematology, biochemistry, and urine samples, including pregnancy test kits, will be provided by the central laboratory contracted by Allergan.

6.6 Summary of Methods of Data Collection

An IVRS/IWRS will be used to screen, randomize, and manage study medication inventory.

Data will be collected using electronic case report form (eCRF) via a validated electronic data capture (EDC) system. Source documents will be used and stored at sites, and may include a patient's medical records, hospital charts, clinical charts, patient chart, copy of the EDC file, as well as the results of diagnostic tests, such as laboratory tests and ophthalmic examinations or tests. A central lab will be used for the analysis of all blood samples. A central reading facility will be used for FA and OCT evaluations.

7. Statistical Procedures

One database lock will occur when all patients have either completed the study or discontinued from the study prematurely. The study will be unmasked for statistical analysis following the database lock. A detailed analysis plan will be approved prior to database lock.

7.1 Analysis Populations

Three analysis populations will be used for statistical analyses: modified intent-to-treat (mITT), per-protocol (PP), and safety.

The mITT population will include all randomized and treated patients with at least 1 postbaseline BCVA measurement. The mITT population will be used for analysis of efficacy variables and baseline characteristics based on the randomized treatment group.

The PP population will include all randomized and treated patients without any significant protocol violations. The PP population will be used to analyze the primary efficacy variable as a secondary efficacy analysis. The PP analysis will be based on the actual treatment that the patients received.

The safety population will include all treated patients. This population will be used for the safety analysis that will be based on the actual treatment that the patients received.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

BCVA measured in the SE using the ETDRS method will be the primary efficacy assessment. For each patient, BCVA data will be collected for both the study and nonstudy eyes at the

screening, day 1/randomization day (prior to the study treatment), and months 1, 2, 3, 5, 6, 7, 9, 10, and 12/exit (or early exit) visits. Analysis of BCVA obtained from the SE will be performed for efficacy. BCVA data from the nonstudy eye will be used only for safety evaluations.

VA will be recorded on the CRF as the number of letters correctly read. For a given eye, the 4-meter distance (standard) of VA will be tested first. If the patient correctly reads at least 20 letters at 4 meters, the VA score will be set as the sum of 30, and the number of letters read correctly. If the patient correctly reads less than 20 letters at 4 meters, the VA will be measured again at 1 meter. The VA score will be set to the number of letters read correctly at 1 meter plus the number of letters read correctly at 4 meters.

BCVA measured at the randomization visit on day 1 prior to the study treatment will be considered as baseline for change from baseline. BCVA data measured at the screening visit will be used for baseline only in the absence of BCVA data at the randomization visit on day 1.

7.2.1 Primary Efficacy Variables

The primary efficacy variable is the average change from baseline in BCVA over the 12-month study period. The average change will be computed by subtracting the baseline BCVA from the area under the BCVA curve (AUC) divided by the total follow-up time for each patient. Calculations for AUC will be based on observed data using the trapezoidal method and will include all postbaseline BCVA data for the patient from the study treatment to the last VA measurement, regardless of scheduled or unscheduled visits.

7.2.2 Secondary Efficacy Variables

Secondary efficacy variables include: $\geq$ 15 letters improvement from baseline in BCVA at month 12; change from baseline in the retinal thickness based on OCT at month 12; and change from baseline in total leakage area based on FA at month 12.

Change From Baseline in Retinal Thickness Based on OCT

OCT is a laser-based diagnostic system providing high-resolution optical sections of the retina. OCT will be performed at the investigators' sites. The OCT images will be transferred to the reading center and evaluated by the retina specialists of the reading center

for the SE. The retinal thickness (microns) in the central 1-mm macular subfield based on OCT will be assessed and analyzed as the secondary efficacy variable.

Change From Baseline in Total Leakage Area Based on FA

FA is a technique to examine the circulation of the retina using the dye tracing method. It involves injection of sodium fluorescein into the systemic circulation, and then an angiogram is obtained by photographing the fluorescence emitted after illumination of the retina. The focal and diffuse leakage area based on FA will be assessed. The total leakage area defined as the sum of focal and diffuse leakage area will be computed and analyzed as the secondary efficacy variable.

7.3 Hypothesis and Methods of Analysis

Unless stated otherwise, analyses for efficacy will be performed using the mITT population based on the 2-sided hypothesis test with a nominal significance level of 0.05.

7.3.1 Primary Efficacy Analyses

The primary efficacy endpoint is the average change from baseline in BCVA in 12 months. The primary analysis will be an analysis of covariance (ANCOVA) comparing the treatment difference in the mean average BCVA change from baseline over a 12-month study period. The ANCOVA model will include the treatment group as the main effect and baseline BCVA score as the covariate.

The null hypothesis is that there is no difference between 700-µg DEX PS DDS and laser in the average BCVA change from baseline in a 12-month period. The alternative hypothesis is that there exists a difference between the 2 treatment groups. The hypothesis test will be based on a 2-sided test at 0.05 significance level. In addition, a 2-sided 95% confidence interval (CI) will be constructed for the difference between the treatment groups in least-square means using the same ANCOVA model. Data collected after receiving any prohibited or standard of care treatments will be excluded from all the efficacy analysis.

7.3.2 Secondary Efficacy Analyses

Analysis for proportion of patients with 15 or more letters improvement from baseline in BCVA at month 12 will be done using a Cochran–Mantel-Haenszel (CMH) test stratified by baseline BCVA categories (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) within each study site.

Analysis for change from baseline in retinal thickness at month 12 will be performed using an ANCOVA model with treatment and baseline BCVA score (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) as the main effects and baseline retinal thickness as the covariate. The between-group difference and the corresponding 2-sided 95% CI in least-square means will be computed using the ANCOVA model. The within-group change from baseline will be analyzed using the paired t-test at the follow-up visits.

Analysis for change from baseline in total leakage area at month 12 will be performed using an ANCOVA model with treatment and baseline BCVA score (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) as the main effects and baseline total leakage area as the covariate. The between-group difference and the corresponding 2-sided 95% CI in least-square means will be computed using the ANCOVA model. The within-group change from baseline will be analyzed using the paired t-test at the follow-up visits.

[redacted]

7.3.4 Safety Analyses

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events and biomicroscopy data.

The number and percent of patients reporting adverse events will be tabulated by primary system organ class, preferred term, and severity for adverse event summarization. The summary tables will be generated separately for adverse events reported during the screening to baseline period (pre-adverse event) and treatment emergent period. Summaries for treatment-emergent adverse events will be organized into the following: all adverse events regardless of causality; treatment-related adverse events; ocular adverse events in the SE; and treatment-related ocular adverse events in the SE.

[redacted]

[redacted]

7.5 Interim Analyses

No interim analysis is planned for this study.

8. Study Visit Schedule and Procedures

The total duration of study participation for each patient is approximately 12.5 months, including screening and randomization/retreatment period. Patients will attend the following

11 visits: screening visit, randomization visit, 8 assessment/retreatment visits, and study exit visit. Please see Table 1 and Figure 1 for a schematic of the schedule of visits and procedures.

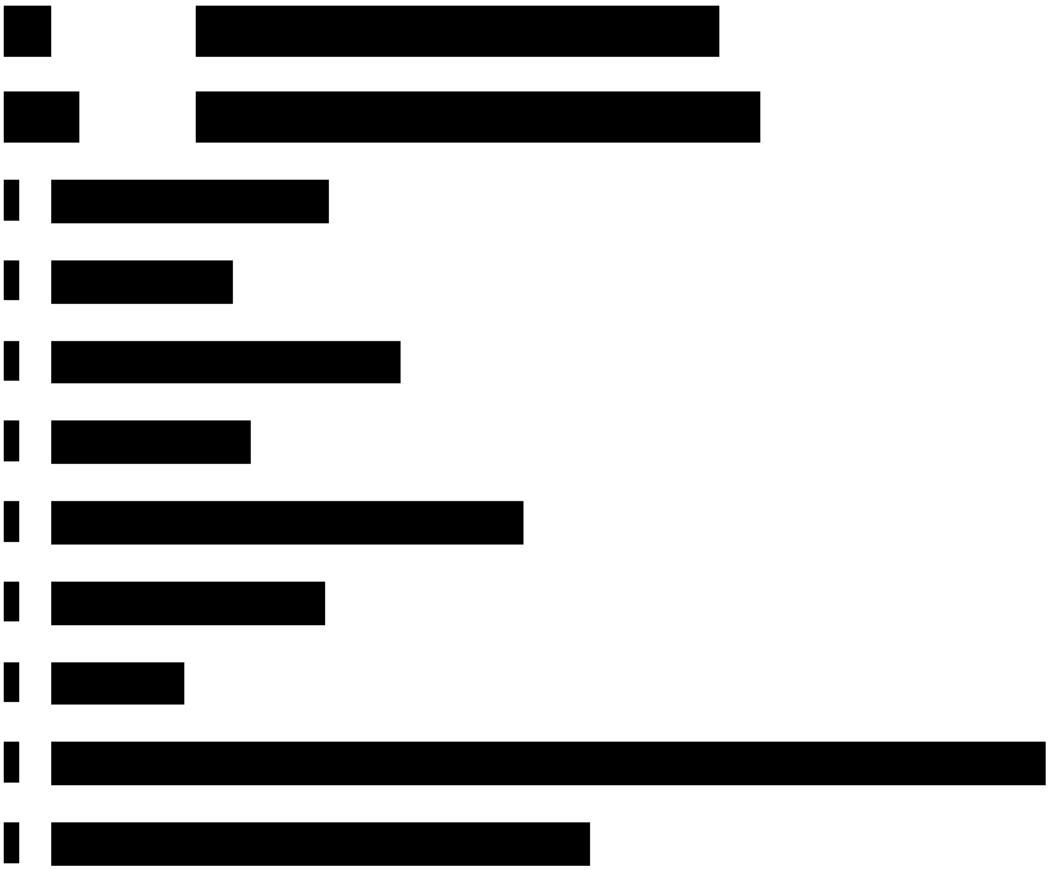
8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective subjects as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study. Prior to patient randomization, patient eligibility must be reviewed and confirmed.

8.1.2 Informed Consent

The study will be discussed with the patient, and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. Each patient that provides informed consent will be assigned a patient number that will be used on patient documentation throughout the study.



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8.3 Instructions for Patients

Patients are instructed to strictly follow the study visit schedule and to report all changes in condition to the investigative site.

8.4 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and well being of patients during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit. For all parameters not measured, "Not Done" should be indicated and the forms should be signed and dated as appropriate.

8.5 Compliance with Protocol

Patients who are inadvertently enrolled, despite significant deviation from protocol-specified inclusion/exclusion criteria, will be followed to monitor patient safety.

Patients will be scheduled for follow-up visits, and these should occur as close as possible to the day specified in the visit schedule.

At each visit after day 1, the investigator will ask patients if they have used any concomitant medications, and have had a procedure performed since the previous visit.

8.6 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate eCRF.

8.7 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Adverse events will be assessed and documented, as appropriate, throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, nondirected question, such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Note: Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event should be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding that cannot be graded

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a

determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event should be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigators Brochure) are to be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 2 months after the last dose of study drug should be immediately reported to an Allergan representative listed on the Allergan personnel page and recorded on the appropriate eCRFs. All patients with a serious adverse event must be followed up, and the outcomes reported. The investigator should supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax using the serious adverse event reporting forms (for serious adverse event fax number, see page 1 of the protocol). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written case history (adverse event report form) that includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

Investigators will be aware of the treatment assignment.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Patients

10.1.1 Compliance with Informed Consent Regulations and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with local regulatory requirements.

There are special situations in which oral informed consent may be taken. Approval to utilize oral consent procedures and instructions on how to properly obtain oral informed consent must be obtained from Allergan personnel.

10.1.2 Compliance With IRB/IEC Regulations

This study is to be conducted in accordance with applicable IRB/IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable local GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator should not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to Allergan, the governing health authorities if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Documentation in accordance with the relevant local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy.

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests, such as x-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRFs serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- patient's name
- patient's contact information
- the date that the patient entered the study, patient number, and patient randomization (or medication kit) number
- the study title and/or the protocol number of the study and the name of Allergan
- the statement that informed consent has been obtained (including the date) prior to any study procedures being performed. A statement that privacy required documentation for this study has been obtained (including the date).
- dates of all patient visits
- medical history, including childbearing potential (if female), height, and weight
- ophthalmic history
- all concurrent medications (List all prescription and nonprescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- vital signs (blood pressure and pulse rate)
- manifest refraction and visual acuity worksheets
- BCVA (source document information for these procedures must be captured and maintained in such a manner that the study personnel performing these examinations do not have access to the remaining study-related information or the source documents for any previous BCVA examinations)
- IOP measurements
- biomicroscopy results
- indirect ophthalmoscopy results
- FA duplicates, as well as backup copies of the electronic records if a digital system is used

- printouts of OCT, as well as backup copies of the electronic records
- occurrence and status of any adverse events
- procedure notes of the study treatment procedure should include the following information: date and time of the procedure, evaluation of the injection site, location of injection to the nearest clock hour, and complications, if any
- date the patient exited the study and a notation as to whether the patient completed the study or reason for discontinuation
- the results of laboratory tests performed by the site (eg, results of urine pregnancy tests)
- all concurrent procedures and concurrent medications (list all prescription and nonprescription medications being taken at the time of enrollment; at each subsequent visit, changes to the list of medications should be recorded)
- any study personnel with knowledge of treatment assignment who shares this information with study personnel with no knowledge of a patient's treatment assignment and/or shares this information with patients; the information shared is to be listed by parameter shared, whom the information was shared with, and the date it was shared

[redacted]

10.4.2 Electronic Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, the Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

The study medications will be packaged, labeled, and supplied by Allergan. All test articles will be identified as an investigational compound and will be labeled with the protocol study number and medication kit number. The label will also specify the storage conditions and state that the study medication is limited to investigational use.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients

in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications/Treatments and /or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by Allergan

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Samples of blood and urine for evaluation of hematology, biochemistry, and urinalysis will be analyzed at a facility meeting Good Laboratory Practice requirements and/or a validated method of quality assurance.

Pharmacokinetic blood samples will be analyzed by a bioanalytical laboratory that meets Good Laboratory Practice requirements. Details about collection and handling of the pharmacokinetic blood samples are provided in the Procedure Manual.

10.8 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory coordinating investigator will be designated prior to the writing of the clinical study report.

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12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

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12.1.2 Pregnancy Test

Females of childbearing potential will have urine pregnancy tests performed. A female is considered to be of childbearing potential unless she is postmenopausal and without menses for 12 months or without a uterus and/or both ovaries. Pregnancy test kits will be administered according to the instructions provided with the tests. A negative pregnancy test result (required for female patients of childbearing potential only) must be obtained at screening and at the day 1 visit before study drug injection. An additional test is required at the month 12/exit visit.

12.1.3 Handling of Biological Specimens

The 10-hour fasting blood and urine samples should be sent to the designated clinical laboratory for analysis on the same day that they are collected.

Details on the collection and handling of pharmacokinetic blood samples are provided in the Procedure Manual.

12.1.4 Visual Acuity Assessment

BCVA will be measured using the ETDRS visual acuity protocol as modified by the Age-related Eye Disease Study Research Group (AREDS report no. 8, 2001). See the Procedure Manual for further details.

12.1.5 Intraocular Pressure

IOP must be measured prior to pupil dilation. Measurements will be taken using a Goldmann applanation tonometer or a hand held tonometer.

12.1.6 Optical Coherence Tomography

The approved equipment for this protocol include the following: the Stratus III (Carl Zeiss Meditec) with software version 4.0 or greater, or Cirrus (Zeiss) or Spectralis (Heidelberg). For sites using the Stratus OCT, at least 6 consecutive radial scans through the macula, each approximately 6 mm in length, will be taken according to Table 1. For sites using the Zeiss Cirrus spectral domain OCT instrument, a Cirrus Macular Cube 512 x 128 scan (128 horizontal scan lines comprised of 512 A-scans) will be required. For sites using the Heidelberg Spectralis OCT instrument images must be acquired in the Volume Scan mode with ART set to 5 (512 by 97 A scans).

Once the OCT instrument has been selected for a patient, that instrument must be used for all the study visits for that patient for the duration of the study.

12.1.7 Biomicroscopic Examination

12.1.7.1 Eyelids

Eyelids will be evaluated for pathology. If pathology is present, it will be described.

12.1.7.2 Conjunctiva (Bulbar or Palpebral)

Hyperemia

None	0	=	Normal, no flush or redness present
Trace	+0.5	=	Minimal flush, reddish color
Mild	+1	=	Mild flush, reddish color
Moderate	+2	=	Bright red color
Severe	+3	=	Deep, bright diffused redness

Edema

None	0	=	Normal, no swelling of the conjunctiva
Trace	+0.5	=	Minimal swelling of the conjunctiva, above normal, which is regional
Mild	+1	=	Mild swelling of the conjunctiva, above normal, which is regional
Moderate	+2	=	General swelling of the conjunctiva
Severe	+3	=	Extensive swelling of the conjunctiva

Subconjunctival Hemorrhage

None	0	=	No hemorrhage
Trace	+0.5	=	Flat and $\leq$ 1 quadrant
Mild	+1	=	Elevated and $\leq$ 1 quadrant, or flat and > 1 quadrant
Moderate	+2	=	Elevated and > 1 but $\leq$ 2 quadrants
Severe	+3	=	Elevated and > 2 quadrants

12.1.7.3 Cornea

Edema

None	0	=	Transparent and clear
Trace	+0.5	=	Trace, localized epithelial haze
Mild	+1	=	Dull glass appearance that may include fine individual microcystic changes
Moderate	+2	=	Dull glass appearance of epithelium with large number of vacuoles with or without stromal edema
Severe	+3	=	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Superficial Punctate Keratopathy

0	=	None
+0.5	=	Trace
+1	=	Mild
+2	=	Moderate
+3	=	Severe

12.1.7.4 Anterior Chamber

For the measurements of cells and flare based on standardized uveitis nomenclature (Jabs et al, 2005), the following settings should be used:

1 x 1 mm slit	High magnification
Highest slit lamp voltage	Low ambient lighting
Illumination angle of 45 degrees	Same grader and slit lamp whenever possible

Cells

0	=	0 cells
+0.5	=	1to 5 cells (trace)
+1	=	6 to15 cells
+2	=	16 to 25 cells
+3	=	26 to 50 cells
+4	=	> 50 cells

Hypopyon

If hypopyon is present, it will be described and the level will be estimated in millimeters.

Flare

None	0	=	No flare seen
Faint	+1	=	Faint flare seen
Moderate	+2	=	Iris and lens details clear
Marked	+3	=	Iris and lens details hazy
Intense	+4	=	Fibrin or plastic aqueous

12.1.7.5 Iris/Pupil

The iris/pupil will be evaluated for pathology. If pathology is present, it will be described.

Rubeosis Iridis

0	=	No visible rubeosis iridis
+0.5	=	Trace visible rubeosis iridis
+1	=	Obvious vessels in 1 quadrant (≤ 90 degrees)
+2	=	Obvious vessels 2 to 3 quadrants (91to 270 degrees)
+3	=	Obvious vessels 4 quadrants (271 to 360 degrees)

Iris Color (screening only)

Iris color will be recorded at screening using the following classification: blue, green, hazel, brown, or other (specify).

12.1.7.6 Lens

Lens Status

Lens status will be assessed as phakic, pseudophakic, or aphakic.

Cataract Assessment (phakic eyes only)

Presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities will be evaluated by comparing biomicroscopic findings with standard photographs (refer to the Procedure Manual for further details). Grades are assigned as follows for each type of opacity:

Opacity is absent
Opacity is present, but less than standard photo #2
Opacity is present and as severe as or worse than standard photo #2

Assessment of Impact of Cataract on Visual Acuity

Assuming that lens opacities were the only vision-limiting condition present in this eye, estimate what the best-corrected distance visual acuity would be based on lens opacities. Assume an undilated pupil and indoor lighting conditions.

None
20/25 ~ 20/40
20/50 ~ 20/100
> 20/100

Posterior Capsule Assessment (aphakic or pseudophakic eyes only)

For aphakic or pseudophakic eyes, the posterior capsule will be assessed and recorded as intact (yes or no).

12.1.8 Fundus Ophthalmoscopic Examination

When possible, for consistency purposes, the same lens(es) should be used for all assessments throughout the study.

12.1.8.1 Macula

The macula will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

12.1.8.2 Optic Nerve

The optic nerve will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

Cup/disc ratio will be reported using a 0.0 to 1.0 scale according to an Armaly chart provided by Allergan. Note if the condition is not evaluable.

12.1.8.3 Vitreous

(1 x 3 mm beam in anterior vitreous) (Opremcak, 1995)

Cells

0	=	None
+0.5	=	1to10 cells
+1	=	11 to 20 cells
+2	=	21 to 30 cells
+3	=	31 to 100 cells
+4	=	> 100 cells

Note if the condition is not evaluable.

Vitreous Haze

The ophthalmologist will grade vitreous haze by viewing the optic disc and posterior retina using the following settings and by comparing the haze against a photographic standardized scale (Nussenblatt et al, 1985) according to the chart provided by Allergan.

Indirect ophthalmoscope and a 20-diopter lens

Illumination set to mid-power

Large beam

Low ambient lighting

Same grader and indirect ophthalmoscope whenever possible

The scale is categorized as follows:

0	=	No inflammation
+0.5	=	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fiber layer [NFL] reflex)
+1	=	Mild blurring of retinal vessels and optic nerve
+2	=	Moderate blurring of optic nerve head
+3	=	Marked blurring of optic nerve head
+4	=	Optic nerve head not visible

Note if the condition is not evaluable.

Vitreous Hemorrhage

Vitreous hemorrhage will be evaluated for severity. Indicate whether or not it is localized to the injection site.

0	=	No visible evidence of hemorrhage on fundus ophthalmoscopic exam
+0.5	=	Retinal detail is visible; trace hemorrhage is present
+1	=	Retinal detail is visible; mild hemorrhage is present
+2	=	Large retinal vessels are visible; central retinal detail is not visible
+3	=	Red reflex is visible; no central retinal detail is seen posterior to the equator
+4	=	No red reflex

Posterior Vitreous Detachment

The presence or absence of a posterior vitreous detachment will be evaluated. Note if the condition is not evaluable.

12.1.8.4 Retina

Retinal Hemorrhage

The presence or absence of a retinal hemorrhage will be evaluated. Note if the condition is not evaluable.

Retinal Tear

The presence or absence of a retinal tear will be evaluated. Note if the condition is not evaluable.

Retinal Detachment

The presence or absence of a retinal detachment will be evaluated. It will be noted if the center of the macula is detached. Note if the condition is not evaluable.

Lattice Degeneration

The presence or absence of lattice degeneration will be evaluated at screening and exit. If present, the condition will be described. Note if the condition is not evaluable.

Round (Atrophic) Retinal Holes

The presence or absence of round retinal holes will be evaluated at screening and exit. If present, the condition will be described. Note if the condition is not evaluable.

12.1.9 Fluorescein Angiography

Early and transit images will be taken of the study eye. Mid- and late-phase images will be taken of the study and nonstudy eye. Angiograms will be read by the study investigator to determine eligibility.

Electronic FA images will be collected for efficacy evaluation by a reading center.

[redacted]

12.1.11 Modified-ETDRS Focal Photocoagulation Technique

The laser treatment "session" should generally be completed in a single "sitting." The photocoagulation treatment technique, as described below, is a modification of the ETDRS technique and is the treatment approach that is commonly used in clinical practice (Modified ETDRS Focal Photocoagulation Technique [Internet], 2006).

Burn characteristic	Direct/grid photocoagulation (modified-ETDRS technique)
Direct treatment	Directly treat all leaking microaneurysms (MA) in areas of retinal thickening between 500 and 3000 microns from the center of the macula (although may treat between 300 and 500 microns of macula if center-involved edema persists after initial focal photocoagulation, but generally not if the visual acuity is better than 20/40)
Change in MA Color with Direct Treatment	Not required, but at least a mild gray-white burn should be evident beneath all MAs
Burn size for direct treatment	50 microns
Burn duration for direct treatment	0.05 to 0.1 sec
Grid treatment	Applied to all areas with edema not associated with MAs. If FA is obtained, grid is applied to areas of edema with angiographic nonperfusion when judged indicated by the investigator
Area considered for grid treatment	500 to 3000 microns superiorly, nasally and inferiorly from center of macula 500 to 3500 microns temporally from macular center; no burns are placed within 500 microns of disc
Burn size for grid treatment	50 microns
Burn duration for grid treatment	0.05 to 0.1 sec
Burn intensity for grid treatment	Barely visible (light gray)
Burn separation for grid treatment	2 visible burn widths apart
Wavelength (grid and focal treatment)	Green to yellow wavelengths

12.2 Glossary of Abbreviations

Term/Abbreviation	Definition
ANCOVA	analysis of covariance
AREDS	Age-Related Eye Disease Study Research Group
BCVA	best-corrected visual acuity
BRB	blood-retinal barrier
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
DEX PS DDS	700-µg extruded dexamethasone posterior segment drug delivery system (extruded drug outside the applicator)
DME	diabetic macular edema
DR	diabetic retinopathy
eCRF	electronic case report form
EDC	electronic data capture system
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IOP	intraocular pressure
ITT	intent-to-treat (population)
IVRS/IWRS	interactive voice/web response system
MA	microaneurysms
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	nonsteroidal anti-inflammatory drugs
OCT	optical coherence tomography
OU	both eyes
PK	pharmacokinetic
PLGA	poly (lactic-glycolic) acid
PP	per-protocol (population)
QID	4 times per day
RVO	retinal vein occlusion
SE	study eye
VA	visual acuity

Term/Abbreviation	Definition
VEGF	vascular endothelial growth factor
[redacted]	[redacted]
WHO	World Health Organization

12.3 Protocol Amendment Summary

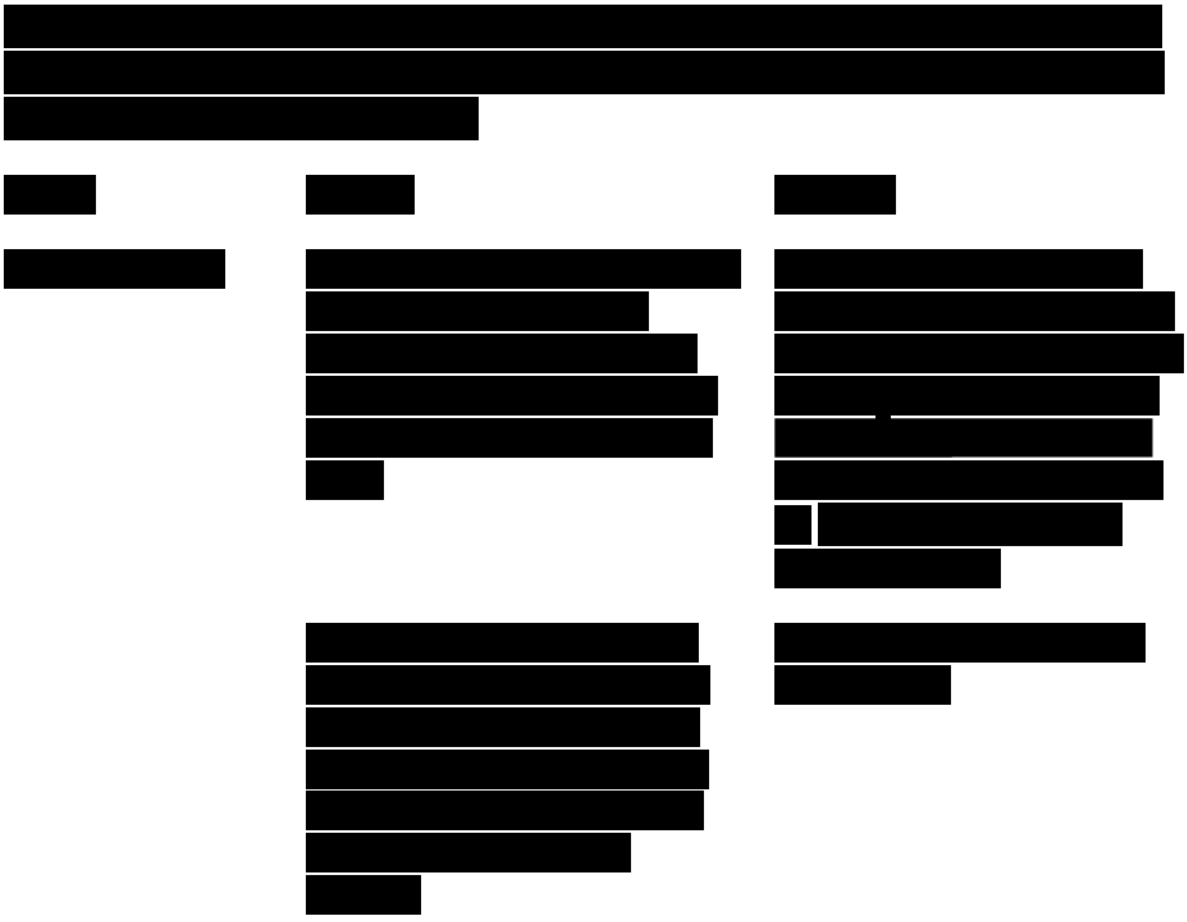
Title: Dexamethasone Posterior Segment Drug Delivery System Versus Laser Photocoagulation in Patients with Diabetic Macular Edema

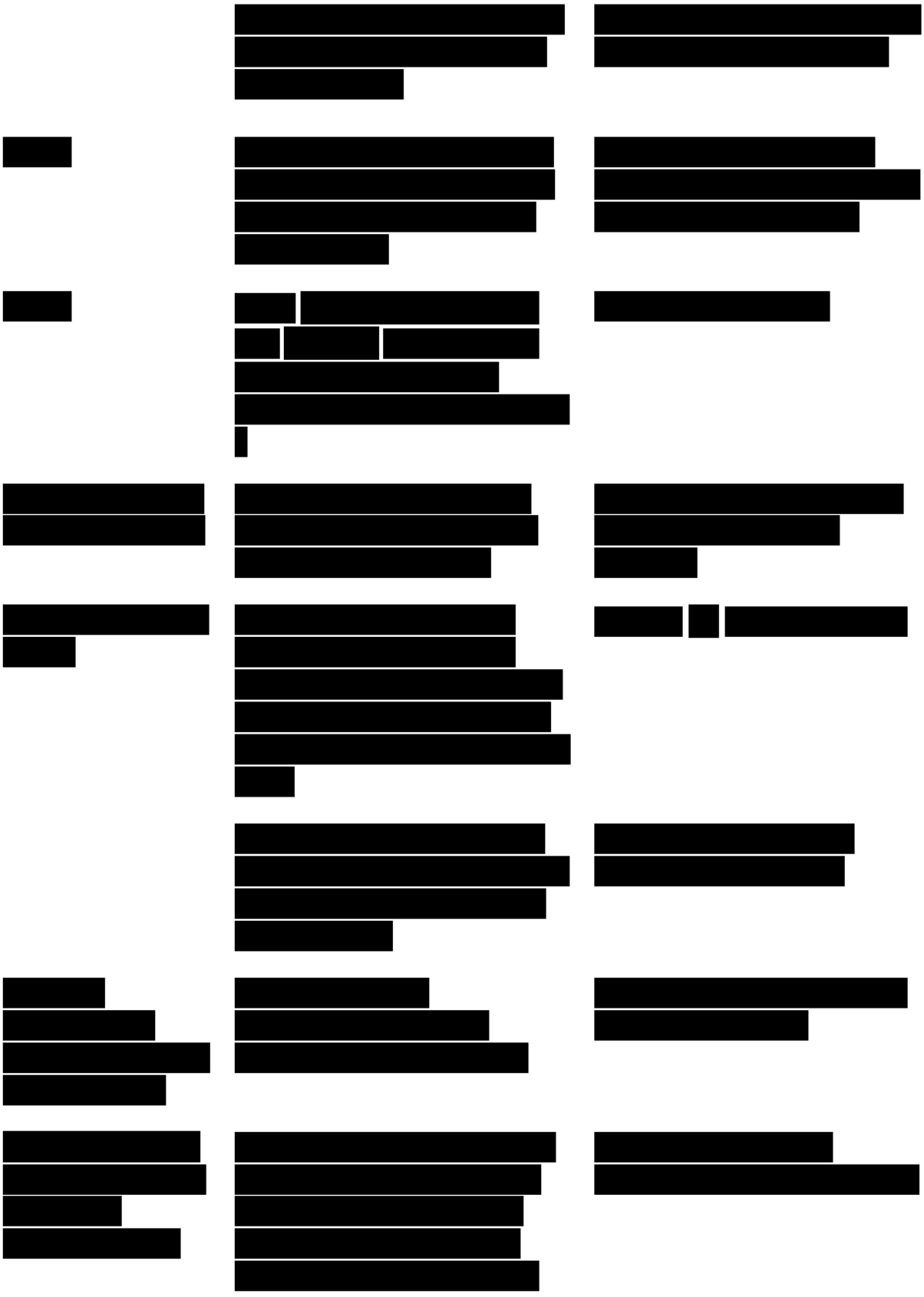
Protocol 206207-026 Amendment 1

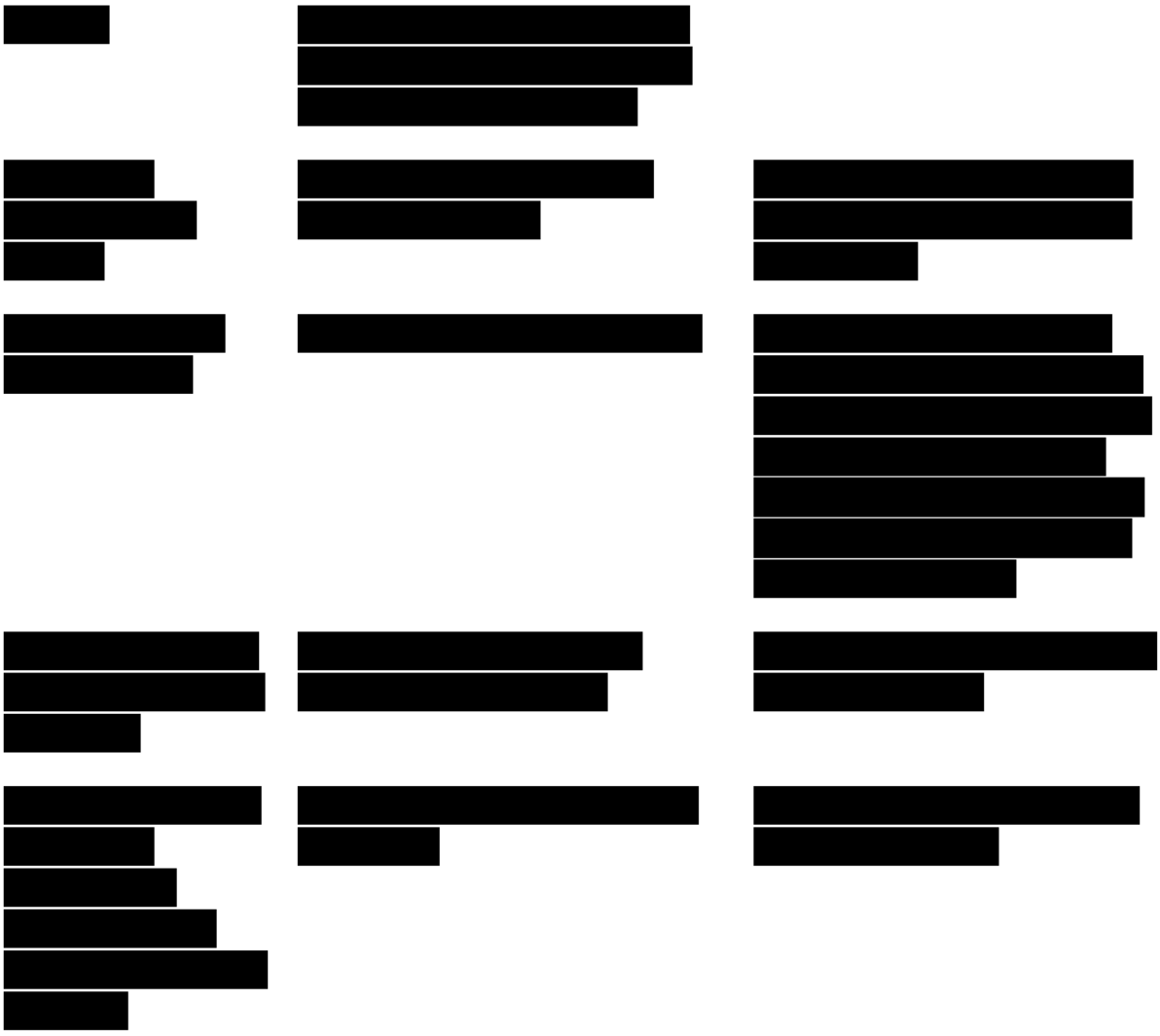
Date of Amendment: April 2013

Amendment Summary

This summary includes changes made to Protocol 206207-026 (approved 01 September 2012). The following key changes were made 1) adding pharmacokinetic analysis; 2) modification of the study sample size.







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Protocol 206207-026 amendment 1

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
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