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Protocol for Study 1491-801-007

Diabetic macular edema; macular edema following branch retinal vein occlusion or central retinal vein occlusion: Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator

VERSION:	3.0	DATE:	29 November 2021
SPONSOR:	AbbVie Inc.	PLANNED NUMBER OF SITES:	Approximately 7 sites in the United States
ABBVIE INVESTIGATIONAL PRODUCT:	Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Implant 0.7 mg	EudraCT:	Not applicable

FULL TITLE: Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator in Participants with Macular Edema due to Retinal Diseases

Incorporating Versions 1.0, 2.0, and 3.0

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator in Participants with Macular Edema due to Retinal Diseases	
Background and Rationale:	The Dexamethasone Posterior Segment Drug Delivery System is approved for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion, for the treatment of noninfectious uveitis affecting the posterior segment of the eye, and for the treatment of diabetic macular edema. AbbVie is updating the Dexamethasone Posterior Segment Drug Delivery System Applicator to include a change of the implant retention feature, other minor changes to the Dexamethasone Posterior Segment Drug Delivery System Applicator (i.e., change of safety tab color, shortening of the safety tab, linkage hole alignment, lever clasp), as well as the change to the visual/physical depth of penetration feature (needle sleeve). No changes are being made to the Dexamethasone Posterior Segment Drug Delivery System Implant.
Objective(s) and Endpoint(s):	The primary objective is to demonstrate that the updated Dexamethasone Posterior Segment Drug Delivery System Applicator (that incorporates the final, to-be-marketed design) delivers the Dexamethasone Posterior Segment Drug Delivery System Implant to the vitreous cavity and is suitable for commercial use in patients with macular edema due to retinal diseases. No secondary objective is defined for this study. No primary or secondary efficacy endpoints are defined for this study. The study is not designed to assess efficacy or safety of the study drug. The Dexamethasone Posterior Segment Drug Delivery System Implant is a Food and Drug Administration-approved drug, and its efficacy and safety are already well established. Safety variables that will be evaluated in the study include vital signs, adverse events, and ocular parameters as determined through assessments of best-corrected visual acuity, biomicroscopic slit lamp examination, ophthalmoscopy, and intraocular pressure. The updated Dexamethasone Posterior Segment Drug Delivery System Applicator performance will be assessed via treatment administration assessment form (completed by the investigator) after Dexamethasone Posterior Segment Drug Delivery System Implant administration. Approximately 54 subjects will be enrolled in this study and randomly assigned in a 2:1 ratio to receive the implant using either the updated applicator (test) or the currently-approved applicator (comparator), respectively.
Investigator(s):	Multicenter.
Study Site(s):	Approximately 7 sites in the United States.

Study Population and Number of Subjects to be Enrolled:	Approximately 54 subjects with macular edema due to retinal vein occlusion (branch retinal vein occlusion or central retinal vein occlusion) or diabetic macular edema will be enrolled in the study; subjects will be randomly assigned in a 2:1 ratio to receive the Dexamethasone Posterior Segment Drug Delivery System Implant using either the updated applicator (test) or the currently-approved applicator (comparator), respectively.
Investigational Plan:	This is a Phase 3b, prospective, randomized, open-label, two-arm, 7-day clinical study in subjects with macular edema due to retinal vein occlusion (branch retinal vein occlusion or central retinal vein occlusion) or diabetic macular edema to support the evaluation of the updated Dexamethasone Posterior Segment Drug Delivery System Applicator (that incorporates the final, to be marketed design) and demonstrate that it delivers the Dexamethasone Posterior Segment Drug Delivery System Implant to the vitreous cavity and is suitable for commercial use in patients with macular edema due to retinal diseases.
Key Eligibility Criteria:	Males and females ≥ 18 years of age with macular edema due to retinal vein occlusion (branch retinal vein occlusion or central retinal vein occlusion) or diabetic macular edema in the study eye. Subjects with no ocular conditions in the study eye for which Dexamethasone Posterior Segment Drug Delivery System Implant is contraindicated.
Study Drug and Duration of Treatment:	Eligible subjects will receive a single intravitreal administration of Dexamethasone Posterior Segment Drug Delivery System Implant 0.7 mg in the study eye on Day 1 using either the updated Dexamethasone Posterior Segment Drug Delivery System Applicator (that incorporates the final, to-be-marketed design or the currently -approved Dexamethasone Posterior Segment Drug Delivery System Applicator in a ratio of 2:1, respectively.
Date of Protocol Synopsis:	29 November 2021

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) is a Food and Drug Administration (FDA)-approved, biodegradable, NOVADUR® solid polymer drug delivery system containing 0.7 mg of dexamethasone. The DEX PS DDS Implant comes preloaded and is delivered in the vitreous cavity by a single-use DEX PS DDS Applicator with a 22 gauge needle that leaves a sutureless self-sealing wound. The sustained release formulation was designed to release dexamethasone from the DEX PS DDS Implant for up to 6 months into the posterior segment of the eye. The DEX PS DDS is approved for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), for the treatment of noninfectious uveitis affecting the posterior segment of the eye, and for the treatment of diabetic macular edema (DME).

AbbVie is updating the DEX PS DDS Applicator to include a change of the implant retention feature, other minor changes to the DEX PS DDS Applicator (i.e., change of safety tab color, shortening of the safety tab, linkage hole alignment, lever clasp), as well as the change to the visual/physical depth of penetration feature (needle sleeve).

There is no defined clinical hypothesis for this study. This study is designed to demonstrate that the updated DEX PS DDS Applicator (that incorporates the final, to be-marketed design) delivers the DEX PS DDS Implant to the vitreous cavity and is suitable for commercial use in patients with macular edema due to retinal diseases. No changes are being made to the DEX PS DDS Implant. As the safety of the DEX PS DDS Implant is already well characterized and is the same as the currently marketed product, the duration of the proposed study is designed to capture investigator experience and any complaints associated with the DEX PS DDS Implant administration using the updated DEX PS DDS Applicator. The planned assessments include best-corrected visual acuity (BCVA), biomicroscopic slit lamp examination, ophthalmoscopy, and intraocular pressure (IOP). Adverse events (AEs) will also be collected. The treatment administration assessment form will be collected to evaluate investigator experience with and performance of the updated DEX PS DDS Applicator and the currently-approved DEX-PS DDS Applicator as a comparator. These parameters are sufficient to determine whether the updated DEX PS DDS Applicator delivers the DEX PS DDS Implant to the vitreous cavity.

2.2 Benefits and Risks to Subjects

The DEX PS DDS Implant was developed to address the problems associated with conventional corticosteroid therapies. The DEX PS DDS Implant administered into the posterior segment of the eye releases a total dose of approximately 0.7 mg dexamethasone. Other routes of administration (topical, periocular, systemic, and standard intravitreal injection of corticosteroid suspensions) require much higher daily doses to deliver equivalent levels of corticosteroid to the posterior segment while also exposing non-target organs to corticosteroids. With DEX PS DDS Implant, substantially lower daily doses of dexamethasone are released directly to the posterior segment, thereby minimizing potential systemic side effects. The DEX PS DDS Implant gradually degrades over time while releasing dexamethasone until it ultimately disappears from the vitreous. Therefore, there is no need to remove the DEX PS DDS

Implant. By delivering a drug directly into the vitreous cavity, the blood-eye barriers are circumvented, and intraocular therapeutic levels can be achieved with minimal risk of systemic toxicity.

The updates being evaluated in this study are related to the DEX PS DDS Applicator only; the DEX PS DDS Implant remains unchanged. The safety of the DEX PS DDS Implant is already well characterized and is the same as the currently marketed product.

Based on the information mentioned above, no additional or new risks are anticipated other than those previously known for DEX PS DDS Implant.

For further details, please see findings from completed studies, including safety data in the current DEX PS DDS investigator's brochure.

Considering the Coronavirus Disease – 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, and given the minimal systemic exposure to the active ingredient, no additional risk to study subjects is anticipated with the use of DEX PS DDS Implant.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective is to demonstrate that the updated DEX PS DDS Applicator (that incorporates the final, to-be-marketed design) delivers the DEX PS DDS Implant to the vitreous cavity and is suitable for commercial use in patients with macular edema due to retinal diseases.

There is no defined clinical hypothesis or estimands for this study.

Secondary

No secondary objective is defined for this study.

3.2 Primary Endpoint

No primary efficacy endpoint is defined for this study. The study is not designed to assess efficacy of the study drug. The DEX PS DDS Implant is an FDA-approved drug, and its efficacy is already well established.

3.3 Secondary Endpoint

No secondary efficacy endpoint is defined for this study. The study is not designed to assess efficacy of the study drug. The DEX PS DDS Implant is an FDA-approved drug, and its efficacy is already well established.

3.4 Additional Endpoints

Additional endpoints are the updated and currently-approved DEX PS DDS Applicator performance (assessed via treatment administration assessment form, completed by the investigator) on Day 1. Further details regarding the treatment administration assessment form are in the Operations Manual (Appendix F).

3.5 Safety Endpoints

This study is not designed to assess safety of the study drug, but AEs will be collected. The DEX PS DDS Implant is an FDA-approved drug, and its safety is already well established.

Safety variables that will be evaluated in the study include vital signs, AEs, and ocular parameters as determined through assessments of BCVA, biomicroscopic slit-lamp examination, ophthalmoscopy, and IOP.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b, prospective, randomized, open-label, two-arm, 7-day clinical study in subjects with macular edema due to retinal vein occlusion (RVO) (BRVO or CRVO) or DME to support the evaluation of the updated DEX PS DDS Applicator (that incorporates the final, to-be-marketed design) and demonstrate that it delivers the DEX PS DDS Implant to the vitreous cavity and is suitable for commercial use in patients with macular edema due to retinal diseases. The schematic of the study is shown in Figure 1. Further details regarding study procedures are in the Operations Manual.

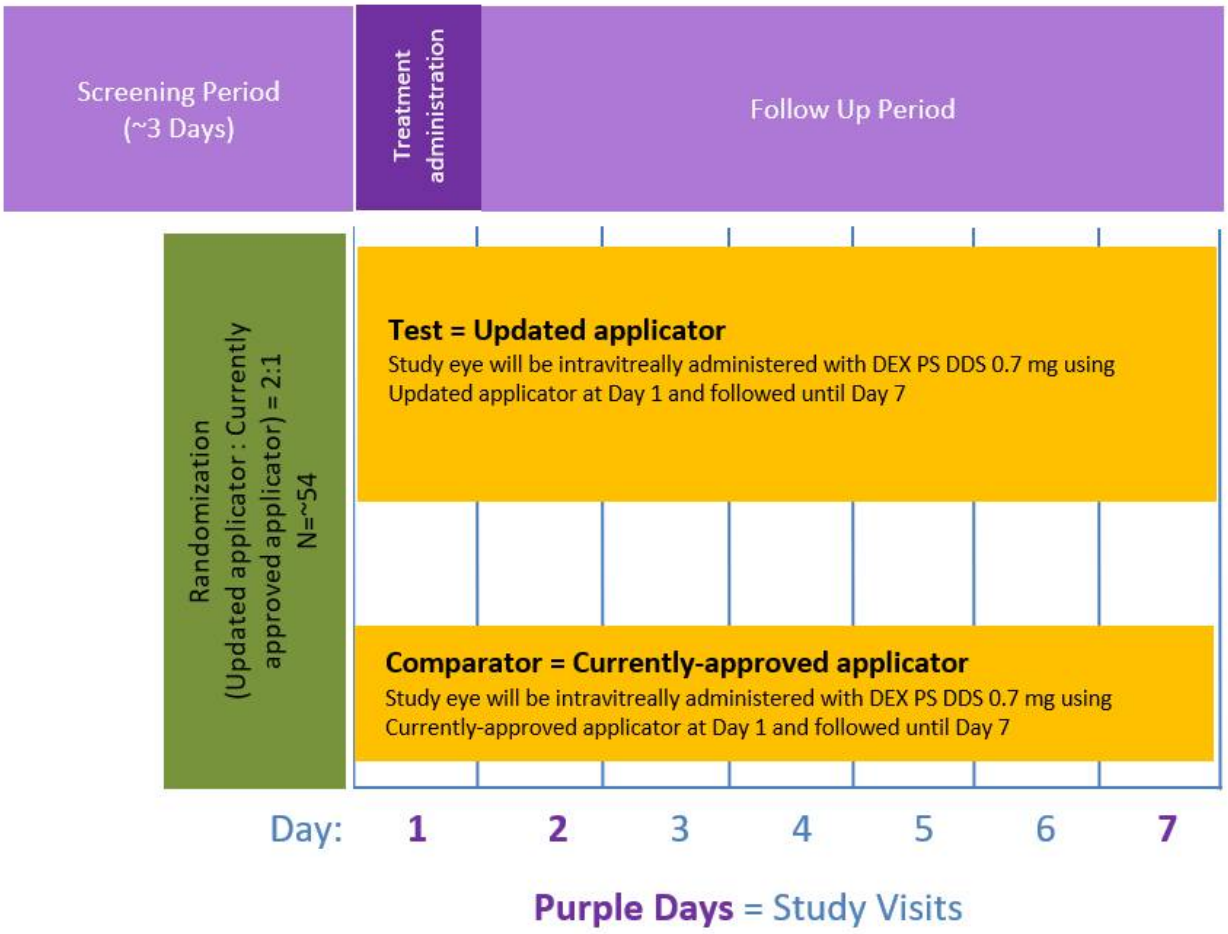
The study will consist of a single administration of the DEX PS DDS Implant (0.7 mg) in the study eye (SE) using either the updated DEX PS DDS Applicator (that incorporates the final, to-be-marketed design) or the currently-approved DEX PS DDS Applicator; approximately 54 subjects will be enrolled in the study and randomly assigned in a 2:1 ratio to receive the DEX PS DDS implant using the updated applicator or the currently-approved applicator, respectively.

Enrollment duration is planned to be approximately 3 months.

See Section 5 for information regarding eligibility criteria.

No interim analysis is planned for this study.

Figure 1. Schematic



DEX PS DDS = Dexamethasone Posterior Segment Drug Delivery System

4.2 Discussion of Study Design

Choice of Control Group

This is a two-arm, open-label study where approximately 54 subjects will be randomized in a 2:1 ratio to receive the same DEX PS DDS implant using either an updated applicator (test arm) or the currently-approved applicator (comparator arm), respectively.

Appropriateness of Measurements

Standard statistical and clinical procedures will be utilized in this study. All measurements in this study are standard for assessing disease activity in subjects with macular edema due to RVO (BRVO or CRVO) or DME. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Adult subjects with macular edema due to RVO (BRVO or CRVO) or DME will be included in this study, consistent with the currently marked product. The SE will be selected by the investigator. Qualified subjects will be administered DEX PS DDS Implant using either the updated or currently-approved DEX PS DDS Applicator in the SE. To avoid confounding results, ocular conditions in the SE in which DEX PS DDS Implant is contraindicated are prohibited during the study.

Selection of Doses in the Study

The study will consist of a single fixed-dose administration of the DEX PS DDS Implant (0.7 mg) in the SE, which is same as the currently marketed product.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all the following criteria to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subject or legally authorized representative must voluntarily **sign and date an informed consent**, approved by an institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 2. Subject is willing to provide written documentation in accordance with the relevant country and local privacy requirements, where applicable.
- 3. In the opinion of the investigator, willing and able to follow study instructions and likely to complete all required study visits.

Demographic and Laboratory Assessments

- 4. Male and female.
- 5. Subject must be ≥ 18 years of age and the legal age of consent, at the time of signing the informed consent.
- 6. Subject is willing and able to comply with procedures required in this protocol.

Disease/Condition Activity

- 7. Diagnosis of
    a. Macular edema due to RVO (BRVO or CRVO) in the SE

    OR

    b. DME in the SE

Subject History

- 8. No ocular conditions in the SE for which DEX PS DDS Implant is contraindicated.
    a. No active or suspected ocular or periocular infections in the SE including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
    b. No glaucoma, with cup to disc ratios of greater than 0.8 in the SE.
    c. No torn or ruptured posterior lens capsule in the SE. Note: Laser posterior capsulotomy in subjects with a pseudophakic eye is not a contraindication for DEX PS DDS Implant use.
    d. No known hypersensitivity to any components of DEX PS DDS Implant.
- 9. No known or suspected allergy or sensitivity to study diagnostic agents or medications.
- 10. Subject does not have a condition and is not in a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with participation in the study.
- 11. The study investigator should consider the subject's overall health condition, including COVID-19 infection, to determine the subject's eligibility to be enrolled in the current study. This should include assessing if the subject is suspected of, quarantined for, or diagnosed with active COVID-19 infection; or whether the subject has any symptoms, as these could be exclusionary based on eligibility criterion 10 above.

Contraception

- 12. For all females of child-bearing potential; a **negative urine pregnancy test** at the Screening/Baseline Visit, prior to study drug administration.
- 13. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 3 months after study drug administration. Female subjects of non-childbearing potential do not need to use birth control.
- 14. Female who is not pregnant or breastfeeding, and is not considering becoming pregnant or donating eggs during the study or for approximately 3 months after study drug administration.

Concomitant Medications

- 15. Subject must not have been treated with any **investigational drug or device** within 30 days prior to study drug administration or is currently enrolled in another clinical study or was previously enrolled in this study.
- 16. Subject is not expected to receive and has not been receiving the following during the study:
    a. SE: intravitreal injections of any sort other than the study treatment
    b. SE: sub-tenon, subconjunctival or topical corticosteroids
    c. SE: anti-vascular endothelial growth factor therapies

d. SE: additional invasive non-study ocular procedures or intraocular surgery (including laser)

e. Systemic corticosteroids (oral, inhaled, intranasal, intravenous, intramuscular, epidural, rectal, or extensive dermal)

f. Systemic immunosuppressants (e.g., cyclosporine), immunomodulators (e.g., interferon), antimetabolites (e.g., methotrexate) or alkylating agents (e.g., cyclophosphamide)

g. Systemic carbonic anhydrase inhibitors (e.g., acetazolamide)

h. Anticoagulants for treatment of ophthalmic vascular disease

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during the study if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND documentation of a follicle-stimulating hormone level ≥ 30 IU/L.

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy during the study and for at least 3 months after study drug administration.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to study Day 1.

- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Day 1.
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device
- Intrauterine hormone-releasing system
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Not applicable for this study.

5.3 Prohibited Medications and Therapy

Prohibited concomitant medications are listed in the eligibility criteria.

During the study, all other investigational drugs are prohibited.

5.4 Prior and Concomitant Therapy

Allowed concomitant medications/therapies are presented in Table 1.

Table 1. Allowed Concomitant Medications/Therapy

Allowed Concomitant Medications/Therapy	Comments/Notes
IOP-lowering treatment	If elevated IOP is observed in the SE after DEX PS DDS Implant administration during the study, IOP lowering treatment will be initiated at the discretion of the investigator.
Medications required for treatment administration	Medications required for DEX PS DDS Implant administration are permitted at the investigator's discretion.
Use of systemic 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 throughout the course of the study.
Treatment in the non-SE	Treatment in the non-SE is not restricted during the study, and the non-SE will receive standard of care per investigator discretion.

DEX PS DDS = Dexamethasone Posterior Segment Drug Delivery System; IOP = intraocular pressure; NSAIDs = nonsteroidal anti-inflammatory drug; SE = study eye

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from Screening/Baseline Visit prior to study drug administration through the Day 7/Premature Discontinuation (PD) Visit.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with DEX PS DDS Implant can be located in the DEX PS DDS investigator's brochure.

Subjects must be able to safely discontinue any prohibited medications as described in the eligibility criteria. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger ribonucleic acid, non-replicating viral vector, protein subunit, etc.) to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may be administered during screening or the study period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of DEX PS DDS Implant on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- Implantation of the DEX PS DDS Implant, when possible, is preferred to be performed at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the Sponsor.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted and continuation of study procedure would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of study procedure would place the subject at risk.
- The subject becomes pregnant before study drug administration.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Subjects should be advised on the continued scientific importance of their data. If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 days. In addition, if subject is willing, follow-up after study drug administration may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

5.7 Study Drug

Study drug will be administered on Day 1, and subjects will not be retreated.

Table 2. Study Drug Identification

Investigational Product	Mode of Administration	Dosage Form	Strength	Manufacturer
Dexamethasone Posterior Segment Drug Delivery System Implant 0.7 mg	Intravitreal Injection – updated applicator	Implant	0.7 mg	Allergan
Dexamethasone Posterior Segment Drug Delivery System Implant 0.7 mg	Intravitreal Injection – currently-approved applicator	Implant	0.7 mg	Allergan

The DEX PS DDS Implant 0.7 mg is supplied in a foil pouch with a single-use updated DEX PS DDS Applicator (that incorporates the final, to-be-marketed design) or the currently-approved single-use DEX PS DDS Applicator. Quantities will be sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit.

All subjects will be treated with DEX PS DDS Implant in an unmasked, open-label manner. Subjects will be randomly assigned in a 2:1 ratio to receive the DEX PS DDS implant using either the updated applicator (test) or the currently-approved applicator (comparator), respectively.

Study drug will be labeled with study kit numbers. The IRT system will provide the designated site personnel with the specific study kit number for each subject after eligibility is confirmed on Day 1. The designated site personnel will receive and maintain the IRT confirmation notifications for each transaction.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying the IRB, regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

Not applicable for this study.

Criteria for subject withdrawal from the study are provided in Section 5.5. Details about reporting adverse events, product complaints, and intercurrent illnesses is provided in Section 4.2 of Appendix F.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form

will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: DEX PS DDS

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE 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 the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported adverse event should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

If an AE, whether associated with DEX PS DDS or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration through study exit will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions reporting for DEX PS DDS in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Event Severity and Relationship to DEX PS DDS

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of DEX PS DDS:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study before planned study drug administration must not receive study drug and must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on safety analyses. Complete and specific details of the statistical analysis will be described in the statistical analysis plan (SAP).

7.2 Definition for Analysis Populations

All subjects who have received DEX PS DDS Implant will contribute to the Safety Analysis Set (SAF). The SAF will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Not applicable for this study.

7.4 Statistical Analyses for Efficacy

This study is not designed to assess efficacy of the study drug. The DEX PS DDS Implant is an FDA-approved drug, and its efficacy is already well established.

Therefore, the efficacy analyses for this study are not applicable.

7.5 Statistical Analyses for Safety

The safety analysis will be performed using the SAF. General safety parameters will include AEs (including pregnancies that meet SAE criteria per Section 6.1) and vital signs. Ocular safety parameters will include BCVA, IOP measurement, biomicroscopy, ophthalmoscopy. The treatment administration assessment form will be collected to evaluate investigator experience with and performance of the updated and the currently-approved DEX PS DDS Applicators.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting AEs will be tabulated based on primary system organ class and preferred terms. Summary tables will be generated for all AEs regardless of causality as well as treatment-related AEs. Descriptive statistics for vital signs will be presented. Ocular safety parameters will be summarized. The treatment administration assessment form will also be summarized.

7.6 Interim Analysis

Not applicable for this study.

7.7 Overall Type I Error Control

Not applicable for this study.

7.8 Sample Size Determination

The sample size is determined empirically based on discussions with FDA to evaluate a minimum of 30 eyes using the updated applicator and a minimum of 15 eyes using the currently approved applicator. Assuming a drop out rate of about 15% and the need to achieve 30 and 15 subjects to use the updated applicator and currently-approved applicator, respectively, the total enrollment would require approximately 54 subjects.

8 ETHICS

8.1 Institutional Review Board (IRB)

The protocol, informed consent form(s) (ICF[s]), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the ICF(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of end of study participation by the last subject in the study.

A subject is considered to have completed the study if he/she has completed all study visits including Day 7.

12 REFERENCES

None.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
COVID-19	Coronavirus Disease – 2019
CRF	Case report form
CRO	Clinical research organization
CRVO	Central retinal vein occlusion
DEX PS DDS	Dexamethasone Posterior Segment Drug Delivery System
DME	Diabetic macular edema
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IOP	Intraocular pressure
IRB	Institutional review board
IRT	Interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	Nonsteroidal anti-inflammatory drugs
OU	Both eyes
PD	Premature discontinuation
PSC	Posterior subcapsular
RSI	Reference safety information
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Study eye

SUSAR	Suspected Unexpected Serious Adverse Reactions

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 1491-801-007: Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator in Participants with Macular Edema due to Retinal Diseases

Protocol Date: 29 November 2021

Clinical research studies sponsored by AbbVie are subject to the ICH GCP and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate IRB, except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Medical Writer	Medical Writing
[redacted]	Medical Monitor	Clinical Development
[redacted]	Study Project Manager	Clinical Study Leadership
[redacted]	Statistical Therapeutic Area Head and Statistics Senior Director	Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the study. The individual activities are described in detail in the Operations Manual. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Study Activities Table

	Screening/ Baseline	Treatment administration	Day 2	Day 7/PD
Activity	Day -3 to Day 1	Day 1	Day 2 + 1d	Day 7 ± 2d
INTERVIEWS & QUESTIONNAIRES				
Informed consent	✓			
Eligibility criteria	✓			
Medical/surgical history (including demographics and ophthalmic history)	✓			
AE assessment	✓	✓	✓	✓
Prior/concomitant therapy (medications and procedures)	✓	✓	✓	✓
Treatment administration assessment form (completed by investigator)		✓		
LOCAL LABS & EXAMS				
Vital signs (blood pressure, pulse rate; at rest ≥ 5 minutes)	✓	✓	✓	✓
Urine pregnancy test (for female subjects of childbearing potential)	✓			
BCVA (Snellen equivalent)	OU		OU	OU
IOP measurement (prior to pupil dilation)	OU		OU	OU
Biomicroscopy exam (slit lamp)	OU		OU	OU
Ophthalmoscopy (indirect)	OU	SE	OU	OU
TREATMENT				
Dispense study drug		✓		
ADMINISTRATION				
Treatment administration (DEX PS DDS Implant 0.7 mg)		SE		

AE = adverse event; BCVA = best-corrected visual acuity; DEX PS DDS = Dexamethasone Posterior Segment Drug Delivery System; IOP = intraocular pressure; OU = both eyes; PD = premature discontinuation; SE = study eye

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	20 April 2021
Version 2.0	24 June 2021

The purpose of Version 3.0 is to update from Version 2.0 the following sections below:

- Minor editorial changes were made throughout the protocol for clarity and consistency.
- On the Title page, the sponsor/emergency medical contact and the number of planned sites were updated.

  Rationale: *Updated due to personnel changes and revised number of planned sites.*
- In Section 1, Section 2.1, Section 3.4, Section 7.5, and Appendix D, treatment administration questionnaire was revised to treatment administration assessment form.

  Rationale: *Revised to be consist with the terminology used on the eCRF.*
- In Section 5.1 (eligibility criteria 7), added that diagnosis of macular edema due to RVO or DME is in the study eye.

  Rationale: *Revised for clarity and accuracy*.
- In Section 5.8, text indicating that subjects could rescreen under their initial screening number was removed.

  Rationale: *Subjects are not to be rescreened using their initial screening number.*
- In Section 5.10, location of criteria for subject withdrawal and adverse event reporting was provided.

  Rationale: *Updated to align with currently approved protocol template.*
- In Section 6.1, details about product complaint reporting were added.

  Rationale: *Added to provide additional information on product complaint reporting.*
- In Section 6.1, removed text indicating that AEs meeting SAE criteria can be reported to CRO.

  Rationale: *AEs meeting SAE criteria are to be reported to AbbVie clinical pharmacovigilance.*
- In Section 8.2, removed text about conduct of the study in the event of a significant disaster/crisis.

  Rationale: *Removed to align with the currently approved protocol template.*
- In Section 11, the end-of-study definition was revised from last subject's last visit to end of study participation by the last subject.

  Rationale: *Revised for clarity and to align with the currently approved protocol template.*

- In Appendix C, list of protocol signatories was updated

  Rationale: *Updated due to personnel changes*

- Appendix F – the Operations Manual was updated as follows
  - In Section 1, the sponsor/emergency medical contact was updated, email address for SAE reporting was updated, and Product Complaints contact information was added.

    Rationale: *Updated due to personnel changes and to align with additional product complaint reporting procedure details added to the protocol.*

  - In Section 2, guidance on timing administration of DEX PS DDS around the SARS-CoV-2 vaccine was added.

    Rationale: *To align with guidance in the protocol.*

  - In Sections 2.1, 3.12, 3.13, and 6.4, treatment administration questionnaire was revised to treatment administration assessment form.

    Rationale: *Revised to be consist with the terminology used on the eCRF.*

  - In Section 2.1, timing of administering the treatment administration assessment form was clarified.

    Rationale: *Timing of administration was clarified for consistency.*

  - In Section 3.7, removed text indicating that the sponsor will provide the pregnancy test kits to sites.

    Rationale: *The sponsor will not be providing the pregnancy test kits.*

  - In Section 3.8, distance from chart was converted from centimeters to inches.

    Rationale: *Revised to be consistent with the use of feet for the Snellen equivalent.*

  - In Section 3.12 (step 12 under Treatment Procedure), instructions to inspect the needle tip were added.

    Rationale: *To align with applicator instructions.*

  - In Section 4.1, text was added to clarify collection of AEs.

    Rationale: *Clarification added to align with currently approved Operations Manual.*

  - In Section 4.2, removed the use of paper SAE CRFs, except as a backup, when reporting SAEs to clinical pharmacovigilance; email address for SAE reporting was updated.

    Rationale: *To discontinue the use of paper SAE CRF forms except for use as a backup and to update contact information.*

  - In Section 4.2, added details about product complaints.

    Rationale: *Product complaints will be collected.*

  - In Section 6.2, additional instructions about storage and disposition of study drug were added.

    Rationale: *To provide additional detail and align with the currently approved Operations Manual.*

- In Section 7.2, subheading for the lens assessment was created.

  Rationale: *To separate out the lens assessment and ophthalmoscopy (indirect).*

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol 1491-801-007

Diabetic macular edema; macular edema following branch retinal vein occlusion or central retinal vein occlusion: Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Implant 0.7 mg

FULL TITLE: Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator in Participants with Macular Edema due to Retinal Diseases

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] MD AbbVie Inc. 2525 Dupont Drive Irvine, California 92612 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Mobile: [redacted] Email: [redacted]
Safety Concerns	Ophthalmology Safety Team 1 North Waukegan Road North Chicago, Illinois 60064	Phone: +1 (833) 942-2226 Email: SafetyManagement_Ophthalmology@abbvie.com
SAE Reporting outside of EDC	Email: IR-Clinical-SAE@abbvie.com	Fax: +1 (714) 796-9504 Back-up: +1 (714) 246-5295
Product Complaints	Email: RD_PQC_QA@abbvie.com	Phone: N/A

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the Coronavirus Disease – 2019 (COVID-19) pandemic. This may include changes such as visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed. Study visits and assessments must be conducted onsite and cannot be conducted virtually during the study.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Study visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed:
  - Day 1 can occur within 3 days of Screening/Baseline (including on the same day).
  - Implantation of the DEX PS DDS implant, when possible, is preferred to be performed at least ± 7 days from the SARS-CoV-2 vaccine administration.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING/BASELINE:

INTERVIEW	• Informed consent • Eligibility criteria • Medical/surgical history (including demographics and ophthalmic history)	• AE assessment • Prior/concomitant therapy (medications and procedures)
EXAM	• Vital signs • BCVA (Snellen equivalent) (OU) • IOP measurement (prior to pupil dilation) (OU) • Biomicroscopy exam (slit lamp) (OU)	• Ophthalmoscopy (indirect) (OU) • Urine pregnancy test (for female subjects of childbearing potential)

AE = adverse event; BCVA = best-corrected visual acuity; IOP = intraocular pressure; OU = both eyes

NOTE: All screening procedures must be performed onsite. Screening/Baseline and Day 1 visits may be performed on the same day.

DAY 1:

INTERVIEW	• AE assessment • Prior/concomitant therapy (medications and procedures) • Treatment administration assessment form, which will be performed following study drug administration (completed by investigator)
EXAM	• Vital signs • Ophthalmoscopy (indirect) (SE)
Rx TREATMENT AND ADMINISTRATION	• Dispense study drug • Treatment administration (DEX PS DDS Implant 0.7 mg) (SE)

AE = adverse event; DEX PS DDS = Dexamethasone Posterior Segment Drug Delivery System; SE = study eye

NOTE: All Day 1 procedures must be performed onsite. Screening/Baseline and Day 1 visits may be performed on the same day.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

DAY 2:

INTERVIEW	• AE assessment • Prior/concomitant therapy (medications and procedures)
EXAM	• Vital signs • BCVA (Snellen equivalent) (OU) • IOP measurement (prior to pupil dilation) (OU) • Biomicroscopy exam (slit lamp) (OU) • Ophthalmoscopy (indirect) (OU)

AE = adverse event; BCVA = best-corrected visual acuity; IOP = intraocular pressure; OU = both eyes

NOTE: All Day 2 procedures must be performed onsite.

DAY 7/PD:

INTERVIEW	• AE assessment • Prior/concomitant therapy (medications and procedures)
EXAM	• Vital signs • BCVA (Snellen equivalent) (OU) • IOP measurement (prior to pupil dilation) (OU) • Biomicroscopy exam (slit lamp) (OU) • Ophthalmoscopy (indirect) (OU)

AE = adverse event; BCVA = best-corrected visual acuity; IOP = intraocular pressure; OU = both eyes; PD = premature discontinuation

NOTE: All Day 7/PD procedures must be performed onsite.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject, the benefits and risks anticipated from participation in the study, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative,

the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the study can be found in the informed consent form.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Eligibility Criteria

Eligibility criteria will be assessed at the Screening/Baseline visit (Section 2.1).

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for the eligibility criteria assessment, other than those specified in Section 2.

3.3 Medical/Surgical History

A complete medical/surgical history, including demographics and ophthalmic history, will be documented at the Screening/Baseline visit (Section 2.1). The medical/surgical history will serve as the baseline for clinical assessment.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for the medical/surgical history assessment, other than those specified in Section 2.

3.4 Adverse Event Assessment

Please refer to Section 4.1.

3.5 Prior/Concomitant Therapy (Medications and Procedures)

Prior/concomitant therapy (medications and procedures) will be recorded at visits per Section 2.1 and Section 2.2, according to the Prior and Concomitant Therapy section of the protocol.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for the prior/concomitant therapy (medications and procedures) assessment, other than those specified in Section 2.

3.6 Vital Signs

Vital sign determinations of systolic and diastolic blood pressures and pulse rate will be obtained at visits as specified in Section 2.1 and Section 2.2. Systolic and diastolic blood pressures will be measured by sphygmomanometer after subjects have been at rest (seated) for at least 5 minutes. Blood pressure will be recorded as millimeters of mercury (mmHg). Pulse rate will be measured after the subject has been in a resting state (seated) for at least 5 minutes. Pulse will be counted for 30 seconds, multiplied by 2, and recorded as beats per minute (bpm).

Measurements should be assessed consistently throughout the study.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for vital signs, other than those specified in Section 2.

3.7 Urine Pregnancy Tests

Pregnancy testing should not be performed for postmenopausal women.

A urine pregnancy test will be performed at the Screening/Baseline visit for all female subjects of childbearing potential. Pregnancy test kits will be administered according to the instructions provided with the test kits.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for urine pregnancy tests, other than those specified in Section 2.

3.8 Best-Corrected Visual Acuity (Snellen Equivalent) Assessment

Best-corrected visual acuity (BCVA) will be measured at all visits using a 3 meter, logMAR chart. Best-corrected visual acuity assessments will be performed using the most recent manifest refraction. In order to provide standardized assessments, all BCVA measurements should be consistently performed using the same test distance and lighting conditions throughout the entire study.

The RIGHT eye will be tested first with the manifest refraction in place.

If 3 meters is not available in front of the phoropter, the results of the manifest refraction will be placed in a trial frame and the BCVA measured at 3 m.

The LogMAR chart should be set at approximately eye level to the average height of a seated subject. Mark a spot on the floor (e.g., with tape) that is 10 feet away from the chart. The examiner should

ensure that the subject's head does not move back and forth during testing. After careful instruction, the left eye is occluded, and testing begins with the right eye.

The subject should be told that the chart has letters only and no numbers. If the subject states a number, he/she should be reminded that the chart contains no numbers and the examiner should request a letter in lieu of the number.

Starting at the top line, the subject should be asked to read slowly (at a rate not faster than about 1 letter per second) in order to achieve the best identification of each letter. Do not proceed until the subject has given a definite response. If the subject loses his/her place in reading or the examiner loses his/her place, the examiner should ask the subject to go back to the line where the place was lost. The examiner should never point to the chart or to a specific letter on the chart or read any of the letters on the chart during the test.

When the subject says they cannot read a letter, he/she should be encouraged to guess. If the subject identifies a letter as 1 of 2 or more letters, they should be asked to choose 1 letter. When it becomes evident that no further meaningful readings can be made, despite urging to guess, the examiner should stop the test for that eye.

Each letter is scored as correct or incorrect. Once a subject has identified a letter with a definite single letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response aloud before he/she has read the next letter aloud, then the change should be accepted.

When the subject no longer correctly identifies any letters on a line, stop testing the eye. The BCVA is the lowest line read with 1 or no misses. Record the acuity in Snellen equivalent units (e.g., 20/63). Repeat procedures for the other eye when specified by protocol.

If the BCVA is worse than logMAR 1.0 (20/200), the subject should be moved to 29.5 inches from the chart. The subject should be seated for testing at this distance. Record the acuity as the lowest line read, multiplying the denominator by four, e.g., 20/80 × 4 = 20/320. If no letters can be read, test for Count Fingers, Hand Motion, or Light Perception, and record.

The pinhole method for measuring BCVA is not acceptable.

REPEAT the entire process for the LEFT eye.

Please note, at the 20/50 line, the chart will separate into 3 sets of charts. For testing the right eye, have the subject continue reading down the right chart. The chart on the left side is for testing the left eye and the center chart can be used for refraction.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for BCVA tests, other than those specified in Section 2.

3.9 Intraocular Pressure measurement

Intraocular pressure (IOP) must be measured prior to pupil dilation. Measurements will be taken as specified in Section 2.1 and Section 2.2.

Measurements will be taken using a Goldmann applanation tonometer or a handheld tonometer affixed to a slit-lamp with the subject seated. The subject and slit-lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight fitting neckwear should be loosened. Both eyes will be tested, with the right eye preceding the left eye. The measurer will look through the binocular viewer of the slit lamp at low power. The tension knob will be preset at a low-pressure value (4 to 6 mm Hg). The measurer will follow the image of the fluorescein-stained semicircles while slowly rotating the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the measurer will take his/her fingers off the tension knob and record the IOP reading along with the date and time of day.

A Goldmann applanation tonometer is preferred, however, contact tonometers, including hand-held tonometers are acceptable. In either case, the same tonometer should be used throughout the study for each subject.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for IOP measurement, other than those specified in Section 2.

3.10 Biomicroscopy Exam (Slit lamp)

Biomicroscopic examinations will be performed using a slit lamp at visits as specified in Section 2.1 and Section 2.2. The examinations will include determination of ophthalmic medical observations/complications, evaluation of the condition of the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil, and lens.

See Section 7.1 for more information.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for biomicroscopic examination, other than those specified in Section 2.

3.11 Ophthalmoscopy (Indirect)

Ophthalmoscopic examinations will be performed through a dilated pupil at visits as specified in Section 2.1 and Section 2.2. The examinations will include evaluation of the lens, vitreous, optic nerve, macula, and retina. Presence of DEX PS DDS Implant in the vitreous cavity of the study eye (SE) after implantation will also be evaluated.

See Section 7.3 for more information.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for ophthalmoscopic examination, other than those specified in Section 2.

3.12 Dispense Study Drug and Treatment Administration

On Day 1, study drug will be dispensed and administered to subjects as specified in Section 2.1. The study drug will be administered by the investigator after all other Day 1 procedures are completed (except for the treatment administration assessment form [completed by the investigator] and ophthalmoscopy [indirect], which will be performed following study drug administration). On Day 1, the site personnel will document the date and time study drug was administered to verify compliance.

DEX PS DDS Study Treatment Procedure

Materials needed

- Tropicamide 1% or local equivalent
- Phenylephrine 2.5% or local equivalent
- Tetracaine 0.5% or local equivalent topical anesthetic
- Povidone iodine 5% or local equivalent antiseptic
- Lidocaine 2% or local equivalent subconjunctival anesthetic
- Fluorescein strips
- Sterile surgical field
- Sterile drape
- 27-gauge needles
- 1 mL and 3 mL syringes
- Cotton tip applicators
- Cellulose sponges
- Eyelid speculum
- Caliper
- Toothed forceps

- Drape scissors

Pre-Treatment

Pre-operative antibiotics to SE 4 times daily may be started up to 3 days prior to study drug administration on Day 1.

Preliminary Procedures

On the day of the study procedure:

1. If necessary, perform tonometry using a previously unopened bottle of the topical anesthetic and a sterile fluorescein strip.
2. Dilate the subject's eyes with fresh, previously unopened bottles of dilating drops.
3. It is recommended that the treating investigator perform a dilated exam on the treated eye, paying special attention to the quadrant that is anticipated to be used for the study procedure.

Treatment Procedure Overview

The general order of steps as written is:

- Conjunctival sterilization
- Local anesthesia
- Sterile field set-up (sterile technique)
- Prep
- Drape (sterile gloves)
- Procedure (sterile gloves)

The procedure is written according to the following considerations:

- Assuming that there is no assistant present for the majority of the steps
- To allow adequate time for the local anesthesia to work
- To avoid having the treating investigator re-glove multiple times
- To avoid having the subject's conjunctiva and cornea exposed with the lid speculum for a prolonged period of time
- To avoid having the subject's cornea and conjunctiva exposed to the povidone-iodine prep or local equivalent antiseptic for a prolonged period of time

Treatment Procedure

The exact order of Steps 3 to 17 of the Treatment Procedure is not mandated as long as sterility is maintained and all of the steps are followed in a logical fashion (i.e., prep done before drape). For

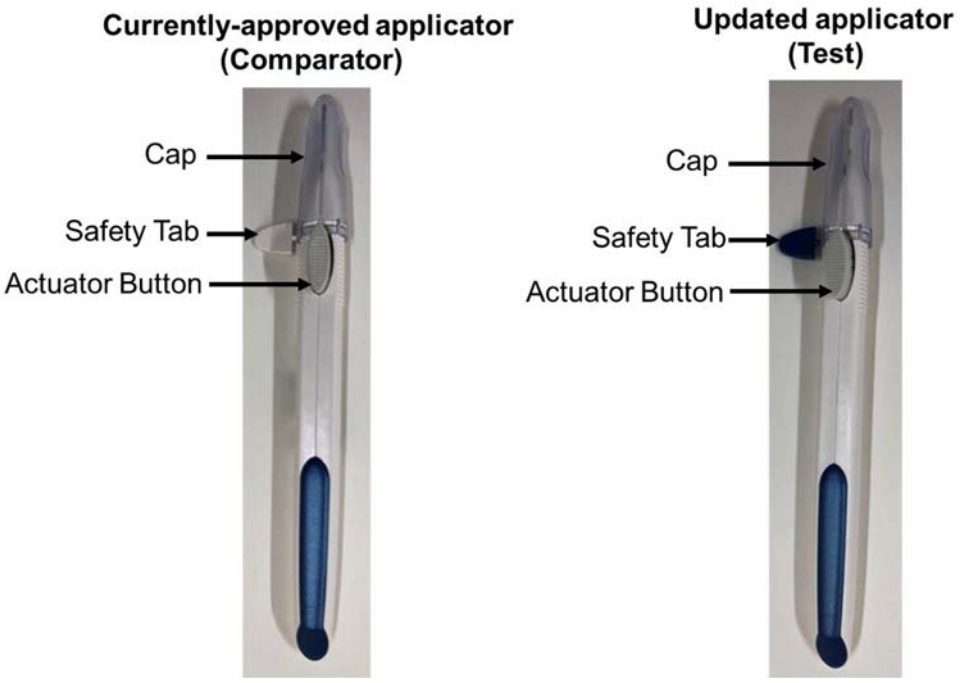
example, if an investigator prefers to give local anesthetic after the prep and drape, it is allowed as long as it is done in a sterile fashion. If an assistant is present, many of the steps can be done in parallel such as the subject prep and the sterile field set-up.

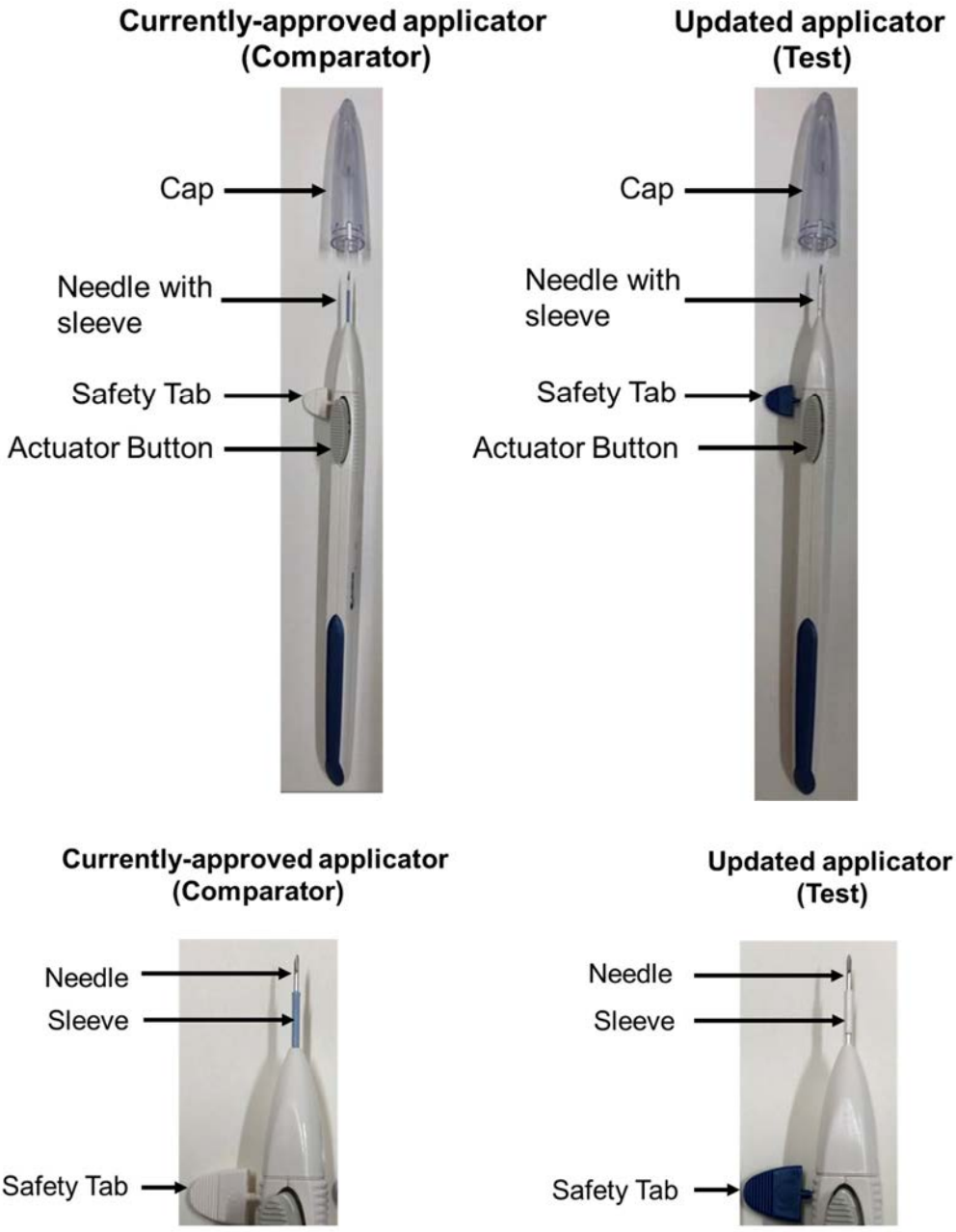
There are two different DEX PS DDS Applicators used in this study, the currently-approved applicator (comparator) and the updated applicator (test). The following instructions applies to both applicators.

1. For all subjects, anesthetize the treated eye with 1 or 2 drops of the freshly opened bottle of topical anesthetic. If the pre-operative antibiotics were not administered prior to Day 1, give an additional 3 doses of antibiotics to the SE every 15 minutes, three times. Irrigate conjunctiva, including fornices, with at least 10 mL of 5% povidone iodine or local equivalent antiseptic.
2. Place 2 drops of the povidone iodine 5% solution or local equivalent antiseptic on the conjunctiva of the treated eye.
3. As needed, using a 27-gauge needle affixed to a 1 mL syringe, inject approximately 0.2 to 0.5 mL of local anesthetic subconjunctivally in the quadrant selected for the study procedure.
    - There is no restriction on where the study procedure can be performed with the exception that 3:00 and 9:00 should be avoided because of the ciliary arteries and nerves. The infero-temporal quadrant is usually the most accessible.
    - Note: if it is your normal practice, the subconjunctival anesthetic may be given after the prep and drape as long as it can be drawn up and administered in a sterile fashion. Additionally, topical anesthetic may also be administered.
4. Open the sterile field.
5. Using sterile technique, open the following onto the sterile field:
    - Sterile eyelid speculum
    - Sterile caliper or 1 mL syringe depending on the surgeon's preference
    - Sterile drape
    - Sterile cotton tip applicators
    - Sterile cellulose sponges
    - Sterile toothed forceps
    - Sterile drape scissors
6. Inspect the foil pouch containing the DEX PS DDS Applicator to ensure the seal is intact.
7. Using sterile technique, open the foil pouch containing the DEX PS DDS Applicator and allow the DEX PS DDS Applicator to gently fall onto the sterile field. Do not drop the DEX PS DDS Applicator onto the field from a great height since that may damage the DEX PS DDS Applicator or dislodge the DEX PS DDS Implant. Remember that only the inside of the foil pouch is sterile.
8. Paint the eyelids, eyelid margins, and lashes of the treated eye 3 times using cotton tip applicators saturated with povidone iodine 5% or local equivalent antiseptic.
9. Place an additional 2 drops of povidone iodine 5% or local equivalent antiseptic on the conjunctiva of the treated eye.

10. If you are using an indirect ophthalmoscope as your coaxial light source, put it on now and adjust it for comfortable viewing. Set it to small pupil (if available) and brightest beam.
11. Put on sterile gloves.
12. Carefully remove the cap by pulling it straight out from the DEX PS DDS Applicator in line with the long axis of the DEX PS DDS Applicator, taking care not to contact the needle with the cap. There is a tube within the cap that closely surrounds the needle, and angling the cap as it is removed can damage the needle or blunt the tip. Inspect the needle tip for damage; the implant retention plug may be visible in the bevel of the updated applicator needle and should not be removed.

Currently-Approved and Updated Applicators:





13. Remove the safety tab from the DEX PS DDS Applicator by pulling it out perpendicular to the long axis of the DEX PS DDS Applicator. Gently place the DEX PS DDS Applicator back on the sterile field taking care to avoid damaging the needle. Do not twist or bend the safety tab to remove it and do not re-cap the DEX PS DDS Applicator.

    - If the indirect ophthalmoscope was used for the visualization or if the treating investigator removed the indirect themselves, first re-glove with sterile glove(s), and then remove the safety tab.

- Note: If the safety tab is not removed prior to the injection, it will be extremely difficult if not impossible to depress the actuator button.

14. Apply the sterile drape to the treated eye so that the eyelashes are excluded from the surgical field. If using a non-fenestrated drape, ask the subject to keep his/her eye open as the drape is applied and use the sterile drape scissors to cut a slit in the drape over the treated eye.
15. Place the sterile speculum between the eyelids of the treated eye. Try to ensure the eyelashes are covered by the drape and are out of the surgical field.
    - If subconjunctival local anesthetic was not given earlier, inject it now and allow it a few minutes to work.
16. Using a sterile caliper or the hub of a 1 cc syringe, measure 4 mm posterior to the limbus in phakic eyes or 3.0-3.5 mm posterior to the limbus in pseudophakic eyes. Avoid 3 and 9 o'clock due to the posterior ciliary arteries and nerves.
17. Displace the conjunctiva away from the injection site and stabilize the globe with sterile toothed forceps (recommended) or a sterile cotton tip applicator.
18. Holding the long axis of the DEX PS DDS Applicator parallel to the limbus, enter the sclera at a shallow tangential angle with the bevel of the needle up (away from the sclera).
19. Staying parallel to the limbus and 4 mm behind the limbus for phakic eyes or 3.0 – 3.5 mm behind the limbus for pseudophakes, advance the tip of the needle partial thickness within the sclera for 1-2 mm (approximately half to all of the bevel) then re-direct the needle towards the center of the vitreous cavity.
20. Advance the needle until the vitreous cavity is entered and the sleeve is against the conjunctiva. Do not advance the needle past the point where the sleeve touches the conjunctiva.
    - Avoid aiming towards the inferior retina. This creates a bi-planar self-sealing needle tract similar to sclerotomies for 23 gauge vitrectomy. When re-directing into the vitreous cavity, allow for the fact that the DEX PS DDS Implant can be up to 5.6 mm long.
21. Slowly depress the actuator button on the DEX PS DDS Applicator until an audible and/or palpable click is noted; on occasion, a smaller, softer click is heard or felt while the button is only partially depressed. Before withdrawing the DEX PS DDS Applicator from the eye, ensure that the button is fully depressed and has locked flush with the DEX PS DDS Applicator surface. Remember that the speed of the DEX PS DDS injection is proportional to the speed that the button is depressed.
22. Withdraw the needle from the eye, back-tracking along the original entry path if possible (first perpendicular then parallel). If an assistant is present, have them use a sterile cotton tip applicator to put pressure on the injection site as the needle exits (as with an intravitreal gas injection).
    - Remember that the subject is only under subconjunctival anesthesia and is able to move his/her eye, so it is more important to keep control of the globe than it is to put pressure on the injection site as the needle exits.
23. Use a cellulose sponge to check for wound leaks and for vitreous incarceration in the wound. Note the injection site to the nearest clock hour.

24. Slide the conjunctiva back into place.
25. Remove the lid speculum and sterile drape. Clean off the povidone-iodine or local equivalent antiseptic prep.
26. Perform indirect ophthalmoscopy without scleral depression looking to see if the DEX PS DDS Implant is visible, and if there are any signs of procedure-related complications such as vitreous hemorrhage, retinal tears, or retinal detachment. The DEX PS DDS Implant is not always visible immediately post-procedure so do not scleral depress solely to visualize the DEX PS DDS Implant.

Post Treatment

1. Remind subject to use antibiotic drops in SE 4 times daily for the next 3 days.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications to dispense or administer study drug, other than those specified in Section 2.

3.13 Treatment Administration Assessment Form

The treatment administration assessment form, as part of the electronic case report form (eCRF), will be completed by the investigator on Day 1 after study drug administration per Section 2.1.

The investigator will evaluate whether the updated (test) or the currently-approved (comparator) DEX PS DDS Applicator dispensed the DEX PS DDS Implant in the vitreous cavity and performed as intended. The position of the DEX PS DDS Implant in the vitreous cavity will be defined[1] as follows:

- Position 1 (P1) = presence of the DEX PS DDS Implant in contact with pars plana and/or ciliary processes.
- Position 2 (P2) = presence of the DEX PS DDS Implant anterior to the equator but with no part of it in contact with pars plana and/or ciliary processes. Equator is identified based on the location of the vortex veins.
- Position 3 (P3) = presence of the DEX PS DDS Implant posterior to the equator. Equator is identified based on the location of the vortex veins.

If the DEX PS DDS Implant is visible between P2 and P3 positions, then it should be marked as P2.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

There are no pandemic or natural disaster-related protocol modifications for the treatment administration assessment form, other than those specified in Section 2.

3.14 Subject Withdrawal from Study

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

3.15 Unscheduled Visits

An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for tests, at the investigator's discretion. Visits to only retest a lab will not be considered an Unscheduled Visit.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious adverse events (AEs) that could be related to study procedures will be collected from the time the subject signed the study specific informed consent until study drug administration. From the time of study drug administration until 30 days after the last dose of study drug or study treatment, all nonserious and serious AEs will be collected whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported serious adverse events (SAEs) will be collected (nonserious AEs will not be collected).

4.2 Reporting Adverse Events, Product Complaints, and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: IR-Clinical-SAE@abbvie.com
FAX to: +1-714-796-9504 Backup: +1-714-246-5295

abbvie

For safety concerns, contact the Ophthalmology Safety Team at:

Ophthalmology Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_Ophthalmology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MD**
AbbVie Inc.
2525 Dupont Drive
Irvine, California 92612

Contact Information:

Mobile: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting.

In the event of a product complaint occurring, the following procedure needs to be followed:

- Take pictures of the product immediately after the complaint occurs, focusing on the area with a complaint or defect if possible
- Do not discard the product
- Quarantine the product in question in appropriate container (such as a SHARPS container)
- Complete the Product Complaint eCRF within 24 hours of the event
- Hold sample at the site location until disposition or further instructions are provided by Sponsor's Product Complaint Team for possible product return.

For any questions, the site may email the Sponsor's Product Complaint Team at RD_PQC_QA@abbvie.com.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19-related missed visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

Severe acute respiratory syndrome coronavirus 2 infections should be captured as AEs. If the event meets the criteria for a SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All AEs associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the study drug in accordance with global and local guidelines and the Appendix of the Investigator Brochure will serve as the reference safety information (RSI). The RSI in effect at the start of a Development Safety Update Report reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (DEX PS DDS Implant 0.7 mg) will be administered into the SE on Day 1 (Section 2.1).

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system.

6.2 Packaging and Labeling

The DEX PS DDS Implant 0.7 mg will be preloaded in the updated DEX PS DDS Applicator that incorporates the final, to-be-marketed design (test) or the currently-approved DEX PS DDS Applicator (comparator).

Both the updated and currently-approved DEX PS DDS Applicators will be provided in a sealed pouch and the pouch will be contained within a carton.

Both the pouch and the carton will be labeled as required per country requirement. The labels must remain affixed to the pouch and carton. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Study drug must be stored at 15° to 30°C (59° to 86°F).

The study drug is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

Sites are responsible for maintaining the study drug according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 3b, prospective, randomized, open-label, two- arm, 7-day clinical study in subjects with macular edema due to retinal vein occlusion (RVO) (branch retinal vein occlusion [BRVO] or central retinal vein occlusion [CRVO]) or diabetic macular edema (DME) to support the evaluation of the updated DEX PS DDS Applicator (that incorporates the final, to be marketed design) and demonstrate that it delivers the DEX PS DDS Implant to the vitreous cavity and is suitable for commercial use in patients with macular edema due to retinal disease. Eligible subjects will be administered DEX PS DDS Implant 0.7 mg in the SE on Day 1. Approximately 54 subjects will be enrolled in this study and randomly assigned in a 2:1 ratio to receive the DEX PS DDS implant using either the updated applicator (test) or the currently-approved applicator (comparator), respectively.

At the Screening/Baseline visit, all subjects will be assigned a unique subject number using the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the Screening/Baseline visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

Eligible subjects will be administered DEX PS DDS Implant 0.7 mg in the SE on Day 1, in an open-label manner. Approximately 54 subjects will be enrolled in this study and randomly assigned in a 2:1 ratio to receive the DEX-PS-DDS implant using either the updated applicator (test) or the currently-approved

applicator (comparator), respectively. The study drug will be administered by the investigator after all other Day 1 procedures are completed (except for the treatment administration assessment form [completed by the investigator] and ophthalmoscopy [indirect], which will be performed following study drug administration).

7 APPENDICES

7.1 Biomicroscopy Exam (slit lamp)

Biomicroscopic examinations will be performed using a slit lamp. The examinations will include determination of ophthalmic medical observations/complications, evaluation of the condition of the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil, and lens.

Eyelid/Eyelid Margins/Lashes:

Edema

0 (None) = No edema
+0.5 (Trace) = Localized, minimal (trace) swelling
+1 (Mild) = Localized, mild swelling
+2 (Moderate) = Diffuse, moderate swelling
+3 (Severe) = Diffuse, severe swelling

Erythema

0 (None) = No erythema
+0.5 (Trace) = Localized, minimal (trace), flush reddish color
+1 (Mild) = Localized, mild, flush reddish color
+2 (Moderate) = Diffuse reddish color encompassing the entire lid margin
+3 (Severe) = Deep diffuse reddish color of lid margins and superior and/or inferior eyelid

Conjunctiva (Bulbar):

Hyperemia

0 (None) = No hyperemia
+0.5 (Trace) = Minimal (trace) flush, reddish color
+1 (Mild) = Mild flush, reddish color
+2 (Moderate) = Bright red color
+3 (Severe) = Deep, bright, diffuse redness

Edema

0 (None) = No edema
+0.5 (Trace) = Localized, minimal (trace) swelling
+1 (Mild) = Localized, mild swelling
+2 (Moderate) = Diffuse, moderate swelling
+3 (Severe) = Diffuse, severe swelling

Conjunctiva (Palpebral):

Hyperemia

0 (None) = No hyperemia
+0.5 (Trace) = Minimal (trace) flush, reddish color
+1 (Mild) = Mild flush, reddish color
+2 (Moderate) = Bright red color
+3 (Severe) = Deep, bright, diffuse redness

Edema

0 (None) = No edema
+0.5 (Trace) = Localized, minimal (trace) swelling
+1 (Mild) = Localized, mild swelling
+2 (Moderate) = Diffuse, moderate swelling
+3 (Severe) = Diffuse, severe swelling

Cornea:

Edema

0 (None) = No edema
+0.5 (Trace) = Localized, minimal (trace) epithelial haze
+1 (Mild) = Dull glass appearance of epithelium that may include fine localized microcystic changes
+2 (Moderate) = Dull glass appearance of the epithelium with large number of cystic changes with or without stromal edema
+3 (Severe) = Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Punctate Epithelial Staining (includes superficial punctate keratopathy, punctate epithelial erosion, and punctate epithelial keratopathy)

0 = No staining
+0.5 = Trace
+1 = Mild
+2 = Moderate
+3 = Severe

Anterior Chamber:

For the measurements of cells and flare based on Standardized Uveitis Nomenclature (SUN) criteria[2], the following settings should be used:

- 1 x 1 mm slit beam
- High magnification
- Highest slit lamp voltage
- Low ambient lighting

- Illumination angle of 45°
- Same grader and slit lamp whenever possible

The Anterior Chamber will be evaluated, at a minimum, for presence of the following pathologies:

- Cells

  0 = 0 cells
  +0.5 = 1-5 cells (trace)
  +1 = 6-15 cells
  +2 = 16-25 cells
  +3 = 26-50 cells
  +4 = > 50 cells

- Flare

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

- Anterior Synechiae
- Hypopyon – if hypopyon is present provide details and if applicable levels in millimeters (mm)

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 2-3 quadrants (91-270 degrees)
+3 = Obvious vessels 4 quadrants (271-360 degrees)

7.2 Lens Assessment

Lens Status:

Lens status will be assessed as phakic, pseudophakic, or aphakic. The lens (including the posterior capsule when visible, e.g., post-lens extraction) will also be evaluated for pathology. If pathology is present, it will be described.

Cataract Assessment (Phakic eyes only):

Under dilated examination, the presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities will be evaluated according to the Age-Related Eye Disease Study Clinical Lens Grading Protocol. Biomicroscopic findings will be compared with standard photographs. AbbVie will supply the site with a copy of the standard photographs.[3]

Pupils should be dilated to at least 5 mm. The slit lamp should be used at 10x magnification. Grading will be performed as described below.

- Nuclear Sclerosis
  - Adjust the slit beam to a width of 0.3 mm and a height of 8.0 mm.
  - Orient the slit beam at 45º to the viewing axis.
  - Compare the slit lamp appearance with Nuclear Standard Photograph #2. The primary considerations are: the opalescence (reflectance) of the nucleus and the blurring of the normal landmarks, i.e., the dark interval at the center of the nucleus (the "sulcus") and the short, bright bands adjacent to it anteriorly and posteriorly (the "lentils," so named for their somewhat bean-like shape).
  - Standard Photographs. Only Nuclear Standard Photograph #2 is used in grading. Standard Photographs #1 and #3 are provided as examples of lenses that have less and more nuclear sclerosis than Standard Photograph #2.
  - Grading scale

    I. Opacity is absent

    II. Opacity is present, but less than Standard Photograph #2

    III. Opacity is present and as severe as or worse than Standard Photograph #2
- Posterior Subcapsular (PSC) Opacities
  - Use retroillumination and include PSC opacities visible with it.
  - Standard Photographs. Only PSC Standard Photograph #2 is used for grading. PSC Standard Photograph #2 with lines at the borders of the opacity is provided for reference.
  - Grading scale

    IV. Opacity is absent

    V. Opacity is present, but less than Standard Photograph #2

    VI. Opacity is present and as severe as or worse than Standard Photograph #2
- Cortical Opacities
  - Use retroillumination.
  - Include both anterior and posterior cortical opacities that are visible with retroillumination.
  - Combine all opacities and compare total area with Cortical Standard Photograph #2 (about 25% of the visible lens).

- Standard photographs. Only Cortical Standard Photograph #2 is used in grading. Standard #2 with lines at the borders of the opacities is provided for reference.
- Grading scale

  VII. Opacity is absent

  VIII. Opacity is present, but less than Standard Photograph #2

  IX. Opacity is present and as severe as or worse than Standard Photograph #2

Posterior Capsule Assessment (aphakic or pseudophakic eyes only)

When visible, an assessment of the posterior capsule will be performed to determine the location of capsular opacification, if any, and whether the capsular bag is intact.

7.3 Ophthalmoscopy (indirect)

Dilated Fundoscopic Examination

The fundus assessments should be conducted through a dilated pupil. The examinations will include evaluation of the lens, vitreous, optic nerve, macula, and retina. The investigator should note if the pupil dilated normally.

Vitreous:

(1 × 3 mm beam in anterior vitreous).[4]

Cells

0 = None
+0.5 = 1-10 cells
+1 = 11-20 cells
+2 = 21-30 cells
+3 = 31-100 cells
+4 = > 100 cells
Note if the condition is not evaluable.

Vitreous Haze

Vitreous haze will be graded by viewing the optic disc and posterior retina using the following settings and by comparing the haze against a photographic standardized scale[5] according to the chart provided by AbbVie.

- 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 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.

Optic Nerve:

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

Cup/Disc ratio will be reported using a 0.0 to 1.0 scale. It will be noted if the condition is not evaluable.

Macula:

The macula will be evaluated, at a minimum, for the presence or absence of the following pathologies. Note if the condition is not evaluable.

- Intraretinal fluid
- Subretinal fluid
- Intraretinal hemorrhage
- Subretinal hemorrhage
- Rhegmatogenous detachment
- Tractional detachment
- Pigment epithelial detachment

Retina Periphery:

The retina periphery will be evaluated, at a minimum, for presence or absence of the following pathologies. Note if the condition is not evaluable.

- Retinal hemorrhage
- Retinal tear (specify location in clock hours)
- Rhegmatogenous retinal detachment with or without macular detachment
- Tractional retinal detachment with or without macular detachment
- Exudative retinal detachment with or without macular detachment
- Round (atrophic) retinal hole
- Lattice degeneration

8 REFERENCES

1. Sudhalkar A, Kodjikian L, Chhablani J, et al. Intraocular dexamethasone implant position in situ and ocular hypertension. Retina. 2018;38(12):2343-9.
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