

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761142Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency**

Date: May 29, 2020

Reviewer: Silvia Perez-Vilar, PharmD, PhD
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS
Division of Epidemiology I

Deputy Division Director: CAPT Sukhminder K. Sandhu, PhD, MPH, MS
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: UPLIZNA™ (Inebilizumab-cdon)

Application Type/Number: BLA 761142

Applicant/sponsor: Viela Bio

OSE RCM #: 2020-949

Expedited ARIA Sufficiency for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Inebilizumab-cdon (UPLIZNA™, Viela Bio) is a humanized, afucosylated IgG1 kappa (IgG1κ) monoclonal antibody designed to bind the B cell-specific surface antigen CD19 in humans, thereby, depleting B lymphocyte populations that express CD19. The proposed indication is the treatment of adults with Neuromyelitis Optica Spectrum Disorders (NMOSD) (b) (4)

It is a new molecular entity (NME) and is currently not approved or marketed in any country. Prior to the approval of eculizumab (SOLIRIS®, Alexion Pharm) for the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody positive in June 2019,¹ there had been no approved treatments for NMOSD. The proposed dosing regimen for UPLIZNA is intravenous (IV) infusion of 300 mg on treatment days 1 and 15, followed by 300 mg every six months starting six months from the first infusion.² The precise mechanism by which UPLIZNA exerts its therapeutic effects in NMOSD is unknown, but is presumed to involve B-cell depletion and may include the suppression of antibody secretion, antigen presentation, B cell–T cell interaction, and the production of inflammatory mediators. The pharmacokinetics of UPLIZNA in NMOSD patients following IV administration is biphasic with a mean terminal half-life of 18 days.³

The Biologic License Application (BLA) submission included safety data from a double-masked, placebo-controlled, randomized clinical trial and its open label extension. It also included two small phase 1 studies, one in patients with scleroderma and one in multiple sclerosis patients, that were reviewed individually.⁴ The proposed label (as of May 27, 2020) includes warnings and precautions for infusion reactions, infections, immunoglobulin levels, and fetal risk.⁵

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of inebilizumab during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease Control and Prevention 2008, Food and Drug Administration 2014). NMOSD, previously known as Devic disease or neuromyelitis optica (NMO), are rare inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Traditionally considered a variant of multiple sclerosis, NMOSD is now recognized as a distinct clinical entity (Wingerchuk, Lennon

¹ U.S. Food and Drug Administration. SOLIRIS (eculizumab). Label dated June 27, 2019. Accessed on May 12, 2020 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s4311bl.pdf

² UPLIZNA (inebilizumab). Draft clinical review dated February 21, 2020. Division of Neurology 2. U.S. Food and Drug Administration

³ Proposed UPLIZNA labeling dated May 27, 2020

⁴ See footnote 2

⁵ See footnote 3

et al. 2007). The presence of the anti-aquaporin-4 (AQP4) antibody is now a key criterion in the most recent criteria for the diagnosis of NMOSD (Wingerchuk and Weinshenker 2012). In the United States, the prevalence was estimated to be approximately 1–2% that of multiple sclerosis, suggesting that there may be 4000–8000 patients (Mealy, Wingerchuk et al. 2012). NMOSD is up to ten times more prevalent in women than it is in men (Wingerchuk, Lennon et al. 2007, Wingerchuk 2009). The mean age at onset is 39 years, although cases are described in children and elderly people (Wingerchuk, Lennon et al. 2007). Current studies have shown that pregnancy increases the risk of disability in women with NMOSD, and that NMOSD increases the risk of adverse pregnancy outcomes, such as miscarriage and pre-eclampsia (Mao-Draayer, Thiel et al. 2020).

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of inebilizumab. The inebilizumab clinical development required that sexually active women of reproductive potential use an effective form of contraception for the duration of the study (up to six months after the final dose of the investigational product). Despite that, a woman on oral contraceptive medication became pregnant approximately 78 days after her last dose of inebilizumab. Inebilizumab was discontinued. There were no complications during the pregnancy or delivery, or birth defects in the newborn (no detailed information, such as gestational age at delivery were provided).⁶ In animal studies, dose-related effects were observed in a combined fertility and early embryofetal development study conducted in a mouse model that expressed human CD19 (huCD19Tg mouse). Animals that received IV inebilizumab at doses of 0, 3, or 30 mg/kg weekly, beginning 15 days prior to mating and through day 15 of gestation, showed reduced fertility index at both dose levels (LD and HD). The data indicated that the reduced number of pregnancies in mice that had successfully mated was most likely due to early preimplantation loss. No adverse effects were observed on embryofetal development. Dose-related effects were also observed in a pre- and postnatal development study in which pregnant mice received IV doses of inebilizumab every three days from day six of gestation through weaning of the F1 pups. F1 pups from the LD and HD groups showed near total absence of B cells. At the end of the study, B cell levels in F1 pups from the LD and HD groups were similar to control. However, in functional immune testing (TDAR), the pups from the LD and HD groups showed impaired response to immunization. These data indicate that, although at normal levels, B cells did not function normally.⁷

The currently proposed labeling, as of May 27, 2020, includes warnings and precautions for fetal risk (Section 5.4). It states that *“Based on animal data, UPLIZNA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to UPLIZNA even after B-cell repletion. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving UPLIZNA and for at least 6 months after the last dose.”* Section 8.1 (Pregnancy) states:

“Risk Summary

UPLIZNA is a humanized IgG1 monoclonal antibody and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with the use of UPLIZNA in pregnant women. However, transient peripheral B-cell depletion and

⁶ UPLIZNA (inebilizumab). Clinical study report–CD-IA-MEDI-551-1155 dated May 15, 2019. Viela Bio

⁷ UPLIZNA (inebilizumab). Pharmacology/toxicology BLA review and evaluation, April 28, 2020. Reference ID: 4599437. Division of Neurology 2. U.S. Food and Drug Administration

lymphocytopenia have been reported in infants born to mothers exposed to other B cell depleting antibodies during pregnancy. B-cell levels in infants following maternal exposure to UPLIZNA have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown [see Warnings and Precautions (5.2)].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Intravenous administration of inebilizumab-cdon (0, 3, or 30 mg/kg/week) to human CD19 transgenic (huCD19 Tg) male and female mice prior to and during mating and continuing in females through gestation day 15 resulted in no adverse effects on embryofetal development; however, there was a marked reduction in B cells in fetal blood and liver at both doses tested. These results demonstrate that inebilizumab-cdon crosses the placenta and depletes B cells in the fetus.

Intravenous administration of inebilizumab-cdon (0, 3, or 30 mg/kg) to huCD19 Tg mice every three days throughout organogenesis and lactation resulted in depletion of B cells and persistent reductions in immune function (even following repletion of B cells and lasting into adulthood) in offspring at both doses tested. At the end of the lactation period, plasma inebilizumab-cdon levels in offspring were only slightly lower than those in maternal plasma. A no-effect level for immunotoxicity in the offspring was not identified.”

Section 8.3 (Females and Males of Reproductive Potential) states:

“Contraception

Women of childbearing potential should use contraception while receiving UPLIZNA and for 6 months after the last infusion of UPLIZNA.”

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete [General ARIA Sufficiency Template](#).*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: Single-arm pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives. These studies do not require inferential analyses and do not have the sample size requirements of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug is indicated for a rare disease, labeling advises about potential risks in pregnancy due to teratogenic findings in animal data, and a study sufficiently powered for a comparative analysis is not required.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DN2, as of May 12, 2020, for the PMR related to pregnancy outcomes:

"Establish a single-arm pregnancy safety study to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to inebilizumab during pregnancy in patients with Neuromyelitis Optica Spectrum Disorder (NMOSD). Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring and plans for comprehensive data analysis and yearly reporting."

3. REFERENCES

Centers for Disease Control and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved February 3, 2020, from <https://www.fda.gov/media/90160/download>.

Mao-Draayer, Y., S. Thiel, E. A. Mills, T. Chitnis, M. Fabian, I. Katz Sand, M. I. Leite, S. Jarius and K. Hellwig (2020). "Neuromyelitis optica spectrum disorders and pregnancy: therapeutic considerations." Nat Rev Neurol **16**(3): 154-170.

Mealy, M. A., D. M. Wingerchuk, B. M. Greenberg and M. Levy (2012). "Epidemiology of neuromyelitis optica in the United States: a multicenter analysis." Arch Neurol **69**(9): 1176-1180.

Wingerchuk, D. M. (2009). "Neuromyelitis optica: effect of gender." J Neurol Sci **286**(1-2): 18-23.

Wingerchuk, D. M., V. A. Lennon, C. F. Lucchinetti, S. J. Pittock and B. G. Weinshenker (2007). "The spectrum of neuromyelitis optica." Lancet Neurol **6**(9): 805-815.

Wingerchuk, D. M. and B. G. Weinshenker (2012). "The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease." Mult Scler **18**(1): 5-10.

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/s/

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06/02/2020 11:04:07 AM

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 28, 2020

To: Sandra Folkendt
Senior Regulatory Health Project Manager
Division of Neurology II (DN2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Sapna Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): UPLIZNA (inebilizumab-cdon)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761142

Applicant: Viela Bio

1 INTRODUCTION

On June 11, 2019, Viela Bio submitted for the Agency's review a Biologics License Application (BLA) 761142 UPLIZNA (inebilizumab-cdon) injection, for intravenous use. The proposed indication for this BLA is for the treatment for adults with neuromyelitis optica spectrum disorders (NMOSD). UPLIZNA (inebilizumab-cdon) was granted Breakthrough Therapy designation on April 17, 2019. In accordance with this designation, the proposed NMOSD indication qualifies as a serious condition. Viela Bio requests Priority Review for this BLA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on July 18, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for UPLIZNA (inebilizumab-cdon) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft UPLIZNA (inebilizumab-cdon) injection MG received on June 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 18, 2020.
- Draft UPLIZNA (inebilizumab-cdon) Prescribing Information (PI) received on June 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 18, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
05/28/2020 03:11:08 PM
DMPP-OPDP review of inebilizumab-cdon (UPLIZNA) BLA 761142 MG

SAPNA P SHAH
05/28/2020 03:17:18 PM

MARCIA B WILLIAMS
05/28/2020 03:19:10 PM

LASHAWN M GRIFFITHS
05/28/2020 03:21:36 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: May 22, 2020

To: Larry Rodichok, M.D.
Division of Neurology Products (DNP)

Sandra Folkendt, Regulatory Project Manager, (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, (DNP)

From: Sapna Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for UPLINZA™ (inebilizumab-cdon) injection,
for intravenous use

BLA: 761142

In response to the DNP consult request dated July 17, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for UPLINZA™ (inebilizumab-cdon) injection, for intravenous use (Uplinza).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Sandra Folkendt) on May 18, 2020 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 3, 2020 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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SAPNA P SHAH
05/22/2020 10:21:50 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 5, 2020
Requesting Office or Division: Division of Neurology 2 (DN 2)
Application Type and Number: BLA 761142
Product Name and Strength: Uplizna (inebilizumab-cdon) injection,
100 mg/10 mL (10 mg/mL)
Applicant/Sponsor Name: Viela Bio
OSE RCM #: 2019-1317-3
DMEPA Safety Evaluator: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 3, 2020 for Uplizna. Division of Neurology 2 (DN 2) requested that we review the revised label and labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Baugh, D. Label and Labeling Review for Uplizna (BLA 761142). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 18. RCM No.: 2019-1317-2.

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/s/

DENISE V BAUGH
03/05/2020 03:29:58 PM

BRIANA B RIDER
03/05/2020 03:32:02 PM

Clinical Inspection Summary

Date	2/3/2020
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Sandra Folkendt, Regulatory Project Manager Lawrence Rodichok, M.D., Medical Officer Division of Neurology 2 Office of Neuroscience
BLA #	761142
Applicant	Viela Bio
Drug	Inebilizumab injection
NME	Yes
Proposed Indication	Treatment of neuromyelitis optica spectrum disorder
Consultation Request Date	7/23/2019
Summary Goal Date	2/11/2020
Action Goal Date	6/11/2020
PDUFA Date	6/11/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Cree, Pardo-Villamizar, and Villegas were inspected in support of this NDA and covered Protocol CD-IA-MEDI-551-1155. No significant inspectional findings were noted at these sites. Dates of neuromyelitis optica spectrum disorder (NMOSD) attacks were verified, as were the Expanded Disability Status Scale (EDSS) scores. There was no evidence of under-reporting of adverse events at any of the sites. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Inebilizumab injection is a monoclonal antibody being developed to reduce the risk of attacks and worsening disability in adult patients with neuromyelitis optica spectrum disorders (NMOSD) under BLA 761142 (IND 117295).

The sponsor has submitted the results from one Phase 2/3 clinical study, Protocol CD-IA-MEDI-551-1155, to support the efficacy and safety of inebilizumab in reducing the risk of attacks and worsening disability in adult patients with NMOSD.

Protocol CD-IA-MEDI-551-1155

Title: “A double-masked, placebo-controlled study with open-label period to evaluate the efficacy and safety of MEDI-551 (inebilizumab) in adult subjects with neuromyelitis optica and neuromyelitis optica spectrum disorders”

Subjects: 230 (safety population)

Sites: 82 sites; North America (16 sites; US 15, Canada 1), Eastern Europe (26 sites), Asia/Pacific (15 sites), Latin America (9 sites), Middle East/Central Asia (7 sites), Western Europe (5 sites), Africa (2 sites), Australia (2 sites)

Study Initiation and Completion Dates: 1/6/2015 – 10/26/2018 double-blind phase; the open-label phase is ongoing

Data Cut-off: 10/26/2018

Database Lock: 12/18/2018

This was a double-blind (DB), randomized, placebo-controlled study in subjects with neuromyelitis optica spectrum disorders (NMOSD). The double-blind phase of the study has been completed while the open-label phase is ongoing and will continue for a minimum of one year and a maximum of 3 years after the last subject enters the open-label phase (or until regulatory approval in participating country).

There were four phases in this protocol:

Screening Phase: up to 28 days

Double-blind, Randomized Phase: 28 weeks

Subjects were randomized (3:1) to the following:

- Inebilizumab 300 mg IV infusion on Days 1 and 15, or
- Placebo IV infusion on Days 1 and 15

All subjects were premedicated prior to investigational product administration with IV methylprednisolone, oral acetaminophen, and oral diphenhydramine to reduce the risk of infusion-related reactions.

During this phase only, a short course of oral corticosteroids (prednisone 20 mg/day or equivalent) was administered to all subjects starting on the first day of investigational product infusion and continuing for 14 days, followed by a 1-week taper. Available data at the time the study was initiated indicated that maximal B cell depletion occurs after approximately 2-4 weeks of inebilizumab administration; therefore, oral corticosteroids were administered to provide prophylaxis against an NMOSD attack during this time period.

Subjects were followed for a period of 197 days in the double-blind (DB) randomized phase. During this phase, an independent Adjudication Committee (AC) evaluated possible NMOSD attacks. Subjects who experienced an AC-determined attack, or who completed Day 197 without an attack, exited the DB randomized phase and could continue into the open-label phase.

Open-label Phase

Subjects received inebilizumab 300 mg on Day 1 and placebo on Day 15 (for those who had received inebilizumab in the DB randomized phase) or inebilizumab on both Day 1 and 15 (for those who had received placebo in the DB randomized phase). Infusion of a single dose of inebilizumab 300 mg then occurred every 6 months for the remainder of the open-label phase. All subjects were premedicated prior to investigational product administration with IV methylprednisolone, oral acetaminophen, and oral diphenhydramine to reduce the risk of infusion-related reactions.

Safety Follow-up Phase

This was for all subjects discontinuing the DB randomized phase or open-label phase. Subjects continued in this phase for 12 months from the last dose of investigational product.

The *primary efficacy endpoint* was the time to onset of an AC-determined NMOSD attack. One of the key secondary endpoints was the worsening from baseline in Expanded Disability Status Scale (EDSS) score at last visit during the DB randomized phase.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history.

III. RESULTS

1. Bruce Cree, M.D.

Site #2000496

Inspection Dates: 9/9/2019 – 9/12/2019

675 Nelson Rising Ln Ste 221 #3206

San Francisco, CA 94143-0003

At this site for Protocol CD-IA-MEDI-551-1155, 8 subjects were screened, 5 subjects were randomized, 5 subjects completed the double-blind phase and continued into the open-label phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, primary/secondary efficacy endpoint data (NMOSD attack date, EDSS scores).

Subjects [REDACTED] ^{(b) (6)}, both randomized to placebo, experienced protocol-defined NMOSD attacks at this site. The date for these attacks were verified during the inspection. EDSS scores were recorded directly into an electronic tablet during the study. A CD containing EDSS scores was available at the site. Site personnel retrieved the EDSS scores

from the CD and printed them out. The FDA field investigator verified EDSS scores from these paper copies against sponsor data line listings. No discrepancies were identified.

There was no evidence of underreporting of adverse events. Two subjects experienced SAEs at this site, all of which occurred during the open label phase or the safety follow-up phase:

- Subject (b) (6)
 - Urinary tract infection/delirium - open label phase
 - Left leg weakness, pulmonary embolism, and cerebrovascular accident – safety follow-up phase
- Subject (b) (6)
 - Depression – open label phase

Narratives for these SAEs are included in the BLA submission.

2. Carlos Pardo-Villamizar, M.D.

Site #2000492

Inspection Dates: 10/7/2019 – 10/9/2019

600 North Wolfe Street

Baltimore, MD 21287

Michael Levy, M.D. was listed as the clinical investigator for Protocol CD-IA-MEDI-551-1155 at this site. Dr. Levy left this site for another position around July 2019. Carlos Pardo-Villamizar, M.D., who had been a subinvestigator for this study, became clinical investigator at that time. This change was documented in a Form FDA 1572 signed by Dr. Villamizar on 6/24/2019.

At this site for Protocol CD-IA-MEDI-551-1155, 10 subjects were screened, 5 subjects were randomized, and all subjects completed the double-blind phase and continued into the open-label phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary/secondary efficacy endpoint data (NMOSD attack date, EDSS scores).

Subject (b) (6), randomized to placebo, experienced a protocol-defined NMOSD attack at this site. The date for this attack was verified during the inspection. EDSS scores were recorded directly into an electronic tablet during the study. A CD containing EDSS scores was available at the site. Site personnel retrieved the EDSS scores from the CD and printed them out. The FDA field investigator verified EDSS scores from these paper copies against sponsor data line listings. No discrepancies were identified.

There was no evidence of underreporting of adverse events and no SAEs occurred at this site.

3. Julio Perez Villegas, M.D

Site #2000620

Inspection Dates: 10/7/2019 – 10/11/2019

Avenida Grau Cuadra 13

Parque Historia De Lane Medicina Peruana S/n

Lima, Peru

At this site for Protocol CD-IA-MEDI-551-1155, 9 subjects were screened, 9 subjects were randomized, and all subjects completed the double-blind phase and continued into the open-label phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, primary/secondary efficacy endpoint data (NMOSD attack date, EDSS scores).

EDSS scores were recorded directly into an electronic tablet during the study. A CD provided by PPD, the CRO, was available at the site for verification of EDSS scores. No discrepancies were identified. The FDA field investigator confirmed that no subjects at this site had an NMOSD attack.

There was no evidence of underreporting of adverse events and no SAEs occurred at this site.

{See appended electronic signature page}

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/s/

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