

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761149Orig1s000**

**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)  
ARIA Sufficiency Memo**

Date: August 13, 2020

Reviewer: Dinci Pennap, PhD, MPH, MS  
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 Concern

Drug Name: Enspryng™ (Satralizumab)

Application Type/Number: BLA 761149

Applicant/sponsor: Genentech, Inc.

OSE RCM #: 2020-869



## **A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns**

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### **1. BACKGROUND INFORMATION**

#### **1.1. Medical Product**

Satralizumab (Enspryng®) is a humanized recycling monoclonal antibody that targets both membrane-bound and soluble interleukin 6 (IL-6) receptors and prevents the binding of IL-6.<sup>1</sup> Because cytokine IL-6 is thought to be a key driver of Neuromyelitis Optica Spectrum Disorders (NMOSD), triggering the inflammation cascade that leads to neurological damage and disability, the proposed indication for satralizumab is the treatment of (b) (4) adults with NMO/NMOSD to reduce the risk of relapse and associated worsening of disability.

Satralizumab is a second-generation molecular improvement on tocilizumab, a humanized anti-IL-6 receptor IgG1 antibody (an immunosuppressant). Compared to tocilizumab, satralizumab has enhanced pharmacokinetics and antigen-neutralizing properties, such that its therapeutic effect is exerted with less frequency of administration.<sup>2</sup> It is designed to dissociate from IL-6 receptors in a pH-dependent manner and to be released into the bloodstream to bind to the antigen again, thus prolonging its elimination half-life in plasma.<sup>2</sup> For both monotherapy and combination with baseline therapy (azathioprine, mycophenolate mofetil and/or corticosteroids), the proposed dosing regimen is a subcutaneous (SC) injection of 120mg satralizumab at weeks 0, 2, and 4, and thereafter once every 4 weeks. Following 120mg SC injection every 4 weeks, the median effective half-life of satralizumab at steady-state ranged between 22.3 and 30.5 days in the monotherapy study and from 32.0 to 37.4 days in the combination therapy study.<sup>2</sup> The proposed label, as of August 11, 2020, includes warnings and precautions for infections, live vaccines, and elevated liver enzymes, and recommends delaying the use of satralizumab in patients with an active infection.

Based on findings from a phase III study, the FDA granted satralizumab a Breakthrough Therapy Designation for the treatment of NMOSD in December 2018.<sup>3</sup> Satralizumab is currently designated an orphan drug in the U.S., Europe and Japan. On June 29, 2020, Japan approved satralizumab for the treatment of NMOSD in adult and pediatric patients.<sup>4</sup> Satralizumab is currently under review at the FDA and EMA.

#### **1.2. Describe the Safety Concern**

As part of a Biologic License Application, the Division of Neurology 2 requested that the Division of Epidemiology assess the sufficiency of the FDA's Active Risk Identification and Analysis (ARIA) for broad-based signal detection studies of satralizumab use for NMOSD during pregnancy.

The potential risk of inadvertent in-utero exposure to medications is well established and drug-related fetal safety concerns remain unabated among female patients of childbearing potential.<sup>5</sup> In the U.S., the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.<sup>6</sup> Notably, because NMOSD is ten times more prevalent among women than it is among men,<sup>7</sup> and the mean age at onset is 39 years,<sup>8</sup> the potential risk of fetal exposure is heightened among patients receiving treatments for NMOSD. Further, research shows that pregnancy is associated with an increased risk of disability in patients with NMOSD, and NMOSD increases the risk of adverse pregnancy outcomes such as miscarriage,



pre-eclampsia and eclampsia.<sup>9</sup> Aquaporin-4 (AQP4), the most common target antigen in NMOSD, is expressed on placenta in early pregnancy and a variety of immune and cytokine changes in pregnancy may impact pregnancy outcomes in NMOSD patients.<sup>9</sup> Research shows that preeclampsia and fetal loss are more frequent in NMOSD than in controls and relapses continue during pregnancy and increase in frequency postpartum.<sup>9</sup>

There are no data from the use of satralizumab in pregnant women in the clinical trials that assessed monotherapy and combination therapy satralizumab. Women of reproductive potential were required to have a negative result from a serum pregnancy test at screening and to use reliable means of contraception throughout the trial period.<sup>1</sup> In non-clinical studies, pre- and postnatal treatment with up to 50mg/kg/week satralizumab in pregnant monkeys resulted in dose-dependent reductions in T-cell dependent antibody responses to antigenic challenge in infant monkeys. Median maximum titer of IgM and IgG were reduced 15% and 16%, respectively, in low-dose infants, and 30% and 40% in high-dose infants.<sup>10</sup> This immunosuppressive event was not unexpected in view of the intended pharmacologic effect of satralizumab, suggesting that Infants of women treated with satralizumab during pregnancy may be at an increased risk of serious infections or impaired response to vaccination.

In the proposed draft product labeling as of August 11, 2020, the Risk Summary in Sections 5.1 and 8.1 state:

#### 5.1 Infections

An increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with (b) (4) IL-6 receptor antagonists.

The most common infections reported in a randomized clinical trial of patients treated with ENSPRYNG who were not on other chronic immunosuppressant therapies (Study 1), and that occurred more often than in patients receiving placebo, were nasopharyngitis (12%) and cellulitis (10%). The most common infections in patients who were on an additional concurrent immunosuppressant and that occurred more often than in patients receiving placebo were nasopharyngitis (31%), upper respiratory infection (19%), and pharyngitis (12%).

Delay ENSPRYNG administration in patients with an active infection, including localized infections, until the infection is resolved.

#### Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other immunosuppressant therapies. Patients with chronic HBV infection were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with ENSPRYNG. Do not administer ENSPRYNG to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+] or are negative for HBsAg and positive for HB core antibody [HBcAb+], consult liver disease experts before starting and during treatment with ENSPRYNG.

#### Tuberculosis

Tuberculosis has occurred in patients treated with other interleukin-6 receptor antagonists. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ENSPRYNG. (b) (4)





(b) (4) Consider anti-tuberculosis therapy prior to initiation of ENSPRYNG in patients with a history of latent active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. Patients should be monitored for the development of symptoms and signs of tuberculosis with ENSPRYNG, even if initial tuberculosis testing is negative.

## Vaccinations

Live or live-attenuated vaccines should not be given concurrently with ENSPRYNG because clinical safety has not been established. Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines.

## 8.1 Pregnancy

### Risk Summary

There are no adequate data on the developmental risk associated with the use of ENSPRYNG in pregnant women. In an animal reproduction study, no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their offspring, with administration of satralizumab-mwge at doses up to 50 mg/kg/week. (b) (4)

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

### Clinical Considerations

#### Fetal/neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ENSPRYNG in utero [see Warnings and Precautions (5.1)].

### Data

#### Animal Data

Subcutaneous administration of satralizumab-mwge (0, 2, or 50 mg/kg) to monkeys weekly throughout pregnancy resulted in no adverse effects on postnatal development of the offspring; however, immune function was impaired in offspring at both doses. Plasma exposures ( $C_{ave}$ ) in dams at the low and high doses were approximately 3 and 100 times, respectively, that in humans at the recommended monthly maintenance dose of 120 mg.

### 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. <sup>†</sup>
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). <sup>†</sup>

<sup>†</sup> 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 requirement of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug is indicated for a rare disease and its potential to cause fetal harm

during pregnancy is unknown. Thus, a study sufficiently powered for a comparative analysis is not required.

**2.4. Which are the major areas where ARIA is 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. The study being considered for broad-based surveillance is descriptive, without sample size requirements or comparison group. Thus, detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and assess causality.

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 DN2 requests a PMR related to pregnancy outcomes; the proposed language, as of August 11, 2020, is as follows:

“A worldwide 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 ENSPRYNG (satralizumab) during pregnancy in patients with Neuromyelitis Optica Spectrum Disorder (NMOSD). Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures, measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring and plans for comprehensive data analysis.”

## References

1. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381(22):2114-2124.
2. Selmaj K, Selmaj I. Novel emerging treatments for NMOSD. *Neurol Neurochir Pol*. 2019;53(5):317-326.
3. CHUGAI. Chugai's satralizumab receives FDA breakthrough therapy designation for neuromyelitis optica and neuromyelitis optica spectrum disorders. [https://www.roche.com/dam/jcr:0661236f-ed44-4eeb-b5df-b535a532e584/en/181219\\_IR\\_Chugai\\_eSatralizumab\\_BTDT.pdf](https://www.roche.com/dam/jcr:0661236f-ed44-4eeb-b5df-b535a532e584/en/181219_IR_Chugai_eSatralizumab_BTDT.pdf). Published 2018. Accessed 7/28, 2020.
4. Roche. Roche's ENSPRYNG (satralizumab) approved in Japan for adults and children with neuromyelitis optica spectrum disorder. <https://ml-eu.globenewswire.com/Resource/Download/54285134-7391-4510-b50c-593c0c2fcb5c>. Published 2020. Accessed 7/28, 2020.
5. Wyszynski DF, Shields KE. Frequency and type of medications and vaccines used during pregnancy. *Obstetric Med*. 2016;9(1):21-27.
6. Dinatale M. The pregnancy and lactation labeling rule (PLLR). <https://www.fda.gov/media/100406/download>. Published 2016. Accessed 7/28, 2020.
7. Marrie RA, Gryba C. The incidence and prevalence of neuromyelitis optica: A systematic review. *Int J MS Care*. 2013;15(3):113-118.
8. Mealy MA, Wingerchuk DM, Greenberg BM. et al. Epidemiology of neuromyelitis optica in the United States: a multicenter analysis. *Arch Neurol*. 2012;69(9):1176-1180.
9. Shosha E, Pittock SJ, Flanagan E, Weinshenker BG. Neuromyelitis optica spectrum disorders and pregnancy: Interactions and management. *Mult Scler*. 2017;23(14):1808-1817.
10. ENSPRYNG (Satralizumab). *Pharmacology/Toxicology BLA Review and Evaluation Dated August 15, 2019, Division of Neurology 2, U.S. Food and Drug Administration*.

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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)

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Date of This Memorandum: August 10, 2020  
Requesting Office or Division: Division of Neurology 2 (DN 2)  
Application Type and Number: BLA 761149  
Product Name and Strength: Enspryng<sup>a</sup> (satralizumab-mwge) injection,  
120 mg/mL  
Applicant/Sponsor Name: GENENTECH INC  
OSE RCM #: 2019-1732-1  
DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS  
DMEPA Team Leader: Lolita White, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 6, 2020 for Enspryng. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Enspryng (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.<sup>b</sup>

## 2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective because the expiration date format is unclear.

## 3 RECOMMENDATIONS FOR GENENTECH INC

We recommend the following be implemented for this BLA 761149:

- A. Carton labeling and container label
  - 1. Expiration date

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<sup>a</sup> Proposed proprietary name was found conditionally acceptable on October 2, 2019.

<sup>b</sup> Whaley E. Human Factors Study Results and Label and Labeling Review for Enspryng (BLA 761149). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 28. RCM No.: 2019-1383 and 2019-1732.

- a. We previously recommended that you identify the expiration date format you intend to use on the container label and carton labeling. We acknowledge you indicate that you intend use the following format for the expiration date: "MM YYYY". However, you did not indicate whether the month will be expressed in numerical or alphabetical characters. If you intend to proceed with the "MM YYYY" format, we recommend the month is expressed in numerical characters and that a hyphen or space be used to separate the portions of the expiration date.

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

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

**Memorandum**

**Date:** August 7, 2020

**To:** Lawrence Rodichok, M.D.  
Division of Neurology 2 (DNII)

Candido Alicea, Ph.D., Regulatory Project Manager, (DNII)

Tracy Peters, Pharm.D., Associate Director for Labeling, (DNII)

**From:** Aline Moukhtara, Team Leader  
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP Labeling Comments for ENSPRYNG® (satralizumab-mwge)  
injection, for subcutaneous use

**BLA:** 761149

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In response to DNII consult request dated July 28, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for ENSPRYNG® (satralizumab-mwge) injection, for subcutaneous use.

**Labeling:** OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNII (Candido Alicea) on July 28, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on August 4, 2020.

**Carton and Container Labeling:** OPDP has review of the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 6, 2020, and we do not have comments.

Thank you for your consult. If you have any questions, please contact Aline Moukhtara at (301) 796-2841 or [Aline.Moukhtara@fda.hhs.gov](mailto:Aline.Moukhtara@fda.hhs.gov).

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ALINE M MOUKHTARA  
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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: August 4, 2020

To: Alicia Candido  
Regulatory Project Manager  
Division of Neurology I (DNI)

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

From: Sharon W. Williams, MSN, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Aline Moukhtara, RN, MPH  
Team Leader  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): ENSPRYNG (satralizumab-mwge)

Dosage Form and Route: injection, for subcutaneous use

Application  
Type/Number: BLA 761149

Applicant: Genentech

## 1 INTRODUCTION

On June 27, 2019 and August 15, 2019, Genentech submitted for the Agency's review a Biologics License Application (BLA) for ENSPRYNG (satralizumab) for subcutaneous use. The proposed indication for ENSPRYNG (satralizumab) injection, for subcutaneous use is for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

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 I (DNI) on August 16, 2019, for DMPP and July, 28, 2020, for OPDP to review the Applicant's proposed MG and IFU for ENSPRYNG (satralizumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 28, 2020.

## 2 MATERIAL REVIEWED

- Draft ENSPRYNG (satralizumab) injection, for subcutaneous use MG and IFU received on June 11, 2020 and August 15, 2019 respectively, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 28, 2020.
- Draft ENSPRYNG (satralizumab) Prescribing Information (PI) received on August 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 28, 2020.

## 3 REVIEW METHODS

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 and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are 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 and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG and IFU are 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 and IFU 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 and IFU.

Please let us know if you have any questions.

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## Clinical Inspection Summary - Addendum

<b>Date</b>	6/26/2020
<b>From</b>	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Susan Daugherty, Regulatory Project Manager Lawrence Rodichok, M.D., Medical Officer Division of Neurology 2 Office of Neuroscience
<b>BLA#</b>	761149
<b>Applicant</b>	Genentech, Inc.
<b>Drug</b>	Satralizumab
<b>NME</b>	Yes
<b>Proposed Indication</b>	Treatment of neuromyelitis optica spectrum disorders
<b>Priority/Standard Review</b>	Standard
<b>Consultation Request Date</b>	10/9/2019
<b>Summary Goal Date</b>	4/15/2020
<b>Action Goal Date</b>	8/15/2020
<b>PDUFA Date</b>	8/15/2020

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical investigator inspections for Protocol BN40900 (SA-309JG) were completed for two sites (Sites 2541 and 2515) in support of this BLA. The results of those inspections are included in the Clinical Inspection Summary (CIS) entered into DARRTS on 4/6/2020. This is a follow up memo to the CIS (b) (4)

(b) (4)

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## II. BACKGROUND

Satralizumab for subcutaneous injection is being developed by Genentech, Inc. under BLA 761149 (IND 118183) for the treatment of neuromyelitis optica spectrum disorders (NMOSD). The IND was transferred from Chugai Pharmaceutical Co., Ltd., to Genentech, Inc., in April 2019. Chugai Pharmaceutical Co., Ltd. was the sponsor when the clinical studies were conducted.

The sponsor submitted results from two Phase 3 studies, BN40898 (SA-307JG, an add-on study) and BN40900 (SA-309JG, a monotherapy study) to support the efficacy and safety of satralizumab in the treatment of NMOSD.

For both protocols, the primary efficacy endpoint was the time to first protocol-defined MS relapse. Clinical investigators identified subjects with clinical MS relapses, blinded Expanded Disability Status Scale (EDSS) examiners performed EDSS assessments, and the Clinical Endpoint Committee (CEC) adjudicated all clinical relapses to identify relapses meeting pre-specified criteria for protocol-defined MS relapse.

Clinical inspections were requested for Protocol BN40900 only, the monotherapy study. For a summary of these inspections, refer to the CIS entered into DARRTS on 4/6/2020.

## III. RESULTS

(b) (4)





(b) (4)



*{See appended electronic signature page}*

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CONCURRENCE:

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Office of Scientific Investigations

**CONCURRENCE:**

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Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**cc:**

Central Document Room/BLA #761149  
Division of Neurology 2/Division Director/Nicholas Kozauer  
Division of Neurology 2/Medical Team Leader/Paul Lee  
Division of Neurology 2/Medical Officer/Lawrence Rodichok  
Division of Neurology 2/Project Manager/Susan Daugherty  
OSI/Office Director/David Burrow  
OSI/Office Deputy Director/Laurie Muldowney  
OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein  
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro  
OSI/GCPAB Program Analyst/Yolanda Patague

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## HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

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)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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<b>Date of This Review:</b>	April 28, 2020
<b>Requesting Office or Division:</b>	Division of Neurology 2 (DN2)
<b>Application Type and Number:</b>	BLA 761149
<b>Product Type:</b>	Combination product
<b>Drug Constituent Name and Strength</b>	Enspryng <sup>a</sup> (satralizumab-mwge <sup>b</sup> ) injection, 120 mg/mL
<b>Device Constituent:</b>	Pre-filled syringe
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Genentech, Inc.
<b>Submission Date:</b>	June 27, 2019; August 15, 2019; August 16, 2019; November 18, 2019; December 4, 2019; January 21, 2020
<b>OSE RCM #:</b>	2019-1383; 2019-1732
<b>DMEPA Safety Evaluator:</b>	Ebony Whaley, PharmD, BCPPS
<b>DMEPA Team Leader:</b>	Lolita White, PharmD
<b>DMEPA Associate Director for Human Factors:</b>	QuynhNhu Nguyen, MS

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<sup>a</sup> Proposed proprietary name was found conditionally acceptable on October 2, 2019.

<sup>b</sup> The nonproprietary name satralizumab-mwge found conditionally acceptable on March 3, 2020.

## 1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761149 for Enspryng (satralizumab-mwge) injection. This is a combination product with a proposed prefilled syringe device constituent part that is intended (b) (4) for the treatment of adults with neuromyelitis optica spectrum disorder (NMOSD).

### 1.1. PRODUCT DESCRIPTION

Enspryng (satralizumab-mwge) injection is a single dose pre-filled syringe containing satralizumab 120 mg/mL. Enspryng is intended for subcutaneous administration by patients, caregivers, or healthcare providers (b) (4) in the abdomen or thigh (see Appendix A).

### 1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On May 19, 2017, we completed a review of the Applicant's HF validation study protocol.<sup>c</sup> We identified deficiencies in the proposed HF validation study protocol and communicated them to the Applicant. We note that the original USAN sapelizumab was updated to satralizumab. We also note the proper name suffix "-mwge" found conditionally acceptable on March 3, 2020.

## 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D

<sup>c</sup> Rider, B. Human Factors Protocol Review for SA237 (sapelizumab) injection IND 118183. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 19. RCM No.: 2017-438.

<b>Table 1. Materials Considered for this Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Information Requests Issued During the Review	E
Labels and Labeling	F

### **3. OVERALL ASSESSMENT OF MATERIALS REVIEWED**

The sections below provide a summary of the study design, failures and use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

#### **3.1 SUMMARY OF STUDY DESIGN**

The Applicant completed HF validation study testing which included simulated use testing, post-use interview, knowledge-based assessment, and a final interview (see Appendix D). The study included 63 participants representative of the intended users in the following user groups: trained adult patients (n = 17), untrained adult patients (n = 15), trained caregivers (n = 16), and untrained caregivers (n = 15). Trained participants had an approximately 15 day training decay period prior to HF validation testing. Per the Applicant, this training decay period is representative of once monthly dosing.

#### **3.2 STUDY METHODOLOGY CONCERN**

We identified a study methodology concern regarding the stratification of the education demographics of the study participants. Specifically, we noted that 11 of the 15 untrained patient participants and 13 of the 15 untrained caregiver participants were college-educated, which does not appear to be representative of the intended users.

In response to the Agency's January 14, 2020, the Applicant stated that: (1) a minimum 5:1 female: male distribution for recruited patient users was targeted to reflect the general NMOSD patient population, and (2) there was no pattern of performance differences that can be linked to the differences in educational level.

Our review of the Applicant's response finds the justification given for the education demographics of the participants in the study is reasonable. (See Appendix E).

#### **3.3 RESULTS AND ANALYSES**

Table 2 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

**TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED****Key:** caregiver trained (CT), caregiver untrained (CU), patient trained (PT), patient untrained (PU)

Tasks	Number of, Description of, and Subjective Feedback for Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Remove needle shield/cap	<p><i>n = 3 failures</i></p> <ul style="list-style-type: none"> <li>- 2 participants (CT05 and CU07) did not remove the needle shield, attempted to inject with the needle shield attached, and failed to inject the full dose. CT05 was needle-experienced and noted that the medicine did not go all the way into the injection pad. During the post-task interview, CT05 suggested that the IFU step should stand out more by using a different color for the text. The other participant, CU07, was needle-naïve and reviewed the steps in the IFU prior to and during the injection procedure, but did not notice the step for removing the needle cap. The participant noted that medicine pooled on the injection pad. The participant indicated they did not notice the instruction to remove the needle shield when injecting. The participant also noted that there are many steps prior to inserting the needle.</li> <li>- 1 participant (PT11) inadvertently removed the plunger from the PFS while attempting to remove the needle shield. The participant rotated the plunger while inspecting the PFS, and then proceeded to try to remove the needle shield with their other hand while still holding the plunger. Instead of the needle shield being removed, the plunger came out of the syringe and the participant attempted to reinsert the plunger. The participant did not refer to the IFU. The participant was given a new device and was successful.</li> </ul>	<ul style="list-style-type: none"> <li>- 1 participant (CT05) forgot to perform the task due to being nervous and also did not fully read the IFU.</li> <li>- 1 participant (CU07) skipped ahead because of the number of steps before inserting the needle in the skin. The Applicant also noted that the participant made a general comment about lack of experience in giving injections. CU07 also did not go through full IFU.</li> </ul> <p>The Applicant did not provide additional root cause information.</p>	<p>The Applicant determined that failures with this task have a low probability of occurrence in real life as typically a stinging sensation is felt when a needle is inserted. The Applicant noted that either the patient or caregiver would notice there is no needle inside the skin or would observe the liquid going out of the syringe and would most likely have corrected the action and/or would perform it correctly in the following injection.</p> <p>The Applicant also indicated that because of the chronic condition of the disease, delayed, incomplete or omitted dose errors would have a negligible impact.</p>	<p>Based on the Applicant's failure modes and effects analysis (FMEA), failure to correctly remove the needle shield could result in dose omission, delayed dose, or incomplete dose. Additionally, if a user pulls out the plunger completely while attempting to remove the needle shield, there is risk of dose omission, delayed dose, and external or mucosal contact with the drug.</p> <p>Our review of the subjective feedback from the HF validation study identified feedback from one participant indicating that the IFU could be improved to increase the prominence of this use task.</p> <p>Our review of the labels and labeling notes that IFU Step 13 instructs users to "...pull the needle cap straight off" and also includes a corresponding graphic. Given this IFU task is not unique to this product and is present with other PFS products and based on</p>

**TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED****Key:** caregiver trained (CT), caregiver untrained (CU), patient trained (PT), patient untrained (PU)

Tasks	Number of, Description of, and Subjective Feedback for Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	<p><i>n = 2 use difficulties/close calls</i></p> <ul style="list-style-type: none"> <li>- 1 participant (PT08) experienced difficulty with removing the needle shield. PT08 initially tried twisting the needle shield before self-correcting and pulling it off. The participant was needle-experienced and believed the needle shield was a "twist off" type.</li> <li>- 1 participant (CU05) experienced a close call when they manipulated the plunger by pulling it back a little and then pushing it forward. The participant said they do this at home to make sure the needle is not clogged. The investigators observed that medication was not expelled when the participant performed this action; only a drop of the medication formed at the tip of the needle.</li> </ul>		<p>The Applicant noted that not removing the needle cap is a known use error with injectable medications.</p> <p>The Applicant did not propose mitigations and determined the residual risk is acceptable and not higher than for similar products.</p>	<p>our overall assessment of the study results and labels and labeling, we find the residual risk acceptable and have no recommendations at this time.</p>
Fully Insert Needle	<p><i>n = 1 failure</i></p> <ul style="list-style-type: none"> <li>- 1 participant (PU10) failed to insert the needle into the injection pad before attempting to depress the plunger and thus did not inject the full dose. The participant held the needle on the surface of the injection pad and began pushing the plunger, which led to the medication pooling on the top of the injection pad. Afterward, the participant indicated they were aware they did not inject all of the medication into the pad. The participant said they were initially concerned that the injection pad was not thick enough for the needle, so they were nervous at first about inserting it into the pad.</li> </ul>	<p>The participant who failed this task was initially concerned that the injection pad was not thick enough for the needle, so they were nervous at first about inserting it into the pad (study artifact).</p> <p>The Applicant did not provide additional root cause</p>	<p>The Applicant determined that failures with this task have a low probability of occurrence as typically needle pain occurs when a needle is injected, and either the patient or caregiver would notice that there is no needle inside the skin and tentatively correct the action.</p>	<p>Based on the Applicant's FMEA, failure to fully insert the needle could result in delayed dose, dose omission, or incomplete dose.</p> <p>Our review of the subjective feedback from the HF validation study did not identify user feedback indicating confusion with the labels and labeling. We also note that the use error may have occurred due to study artifact (i.e. use of an injection pad).</p>



<b>TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED</b> <b>Key:</b> caregiver trained (CT), caregiver untrained (CU), patient trained (PT), patient untrained (PU)				
<b>Tasks</b>	<b>Number of, Description of, and Subjective Feedback for Failures/Use Errors, Close Calls and Use Difficulties</b>	<b>Applicant's Root Cause Analysis</b>	<b>Applicant's Discussion of Mitigation Strategies</b>	<b>DMEPA's Analysis and Recommendations</b>
	<i>n = 1 use difficulty</i> - 1 participant (PU08) experienced difficulty with fully inserting the needle. The participant bent the needle when initially trying to insert it into the injection pad, but readjusted and inserted the needle and was able to complete the remainder of the injection process.	information for the use difficulty.	<p>The Applicant indicated that as per the chronic condition of the disease, the impact of the therapy for this situation is considered negligible.</p> <p>The Applicant did not propose mitigations and determined the residual risk is acceptable.</p>	<p>Our review of the IFU notes that IFU Step 16 appears clear and has a supporting graphic.</p> <p>Based on our overall assessment of the study results and labels and labeling, we find the residual risk acceptable and have no recommendations at this time.</p>
Push Down the Plunger Completely (inject drug)	<i>n = 1 failure</i> - 1 needle-experienced participant (CU11) placed their index finger on the plunger prior to inserting the needle and inadvertently pushed out several drops of medication before inserting the needle into the pad and injecting the remaining medication. The participant referred to the IFU during the injection procedure but did not completely unfold the IFU. They stated during the post-task interview that they did not feel the need to read the IFU step-by-step due to their injection experience.  <i>n = 1 close call</i> - 1 needle-experienced participant (CT07) inserted the needle into the injection pad and then pulled up on the plunger and accidentally removed it from the syringe. The participant then reinserted the plunger and was	- CU11: Applicant determined their performance was due to mental slip associated with negative transfer from previous experience with PFS. The Applicant noted that in the post-task interview, CU11 said they noticed medication dripping from the needle, but that was normal in their experience. They also indicated that their holding	<p>The Applicant stated that the risk was reduced as low as reasonably possible and no further practicable risk control measures could have been implemented.</p> <p>Therefore, the Applicant determined that the residual risk associated to the failure with this task is acceptable when weighted against benefit of the medication and the risks of similar devices.</p>	<p>Based on the Applicant's FMEA, failure to correctly push down the plunger while injecting the drug might result in dose omission, delayed dose, underdose, or unintended needle stick into the patient, 3<sup>rd</sup> party or caregiver.</p> <p>Our review of the subjective feedback from the HF validation study did not identify user feedback indicating confusion with the labels and labeling. We also note that the use error and close may have occurred due to negative transfer (e.g. previous experience with other devices).</p>

<b>TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED</b> <b>Key:</b> caregiver trained (CT), caregiver untrained (CU), patient trained (PT), patient untrained (PU)				
Tasks	Number of, Description of, and Subjective Feedback for Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	able to fully depress the plunger. They stated that they did this because with their injections at home they are used to having to pull back on the plunger first to draw medicine.	technique was also based on experience.  The Applicant did not provide additional root cause information.		Our review of the labels and labeling notes that IFU Step 18 appears clear and has supporting graphics. We also note IFU Step 18 instructs users to push the plunger "all the way down until it touches the activation guards".  Based on our overall assessment of the study results and labels and labeling, we find the residual risk acceptable and have no recommendations at this time.
Release Plunger at the End of the Stroke engages the needle safety device (NSD)	<i>n = 3 failures</i> - Three participants (PU07, PU11, and CT10) did not activate the needle safety device (NSD). Two of the three participants (PU07 and PU11) were needle-experienced and the remaining participant (CT10) was needle-naïve. The participants thought the injection was complete because they pushed the plunger until they felt resistance. The study investigators observed that the participants appeared to have pushed the plunger far enough to deliver a full dose but stopped just prior to triggering the activation guards.  <i>n = 1 use difficulty</i> - One needle-naïve participant (CT03) experienced difficulty activating the NSD. The participant initially	- PU07, PU11, and CT10: Thought the injection was complete because they pushed the plunger until they felt resistance.  - CT03: Initially did not press the plunger far enough to activate the NSD	The Applicant stated that the risk mitigations were implemented during development and residual risks were accepted as this is a known use error and no harmful events have been reported related to this.  The Applicant did not propose mitigations and determined the residual risk is acceptable.	Based on the Applicant's FMEA, failure to release the plunger and engage the needle safety device might result in an unintended needle stick by a used needle into the patient, 3 <sup>rd</sup> party, or caregiver.  Our review of the subjective feedback from the HF validation study did not identify user feedback indicating confusion with the labels and labeling. However, we note that the participants who failed this task believed they had completed the task due to feeling resistance on when pressing the

<b>TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED</b>				
<b>Key:</b> caregiver trained (CT), caregiver untrained (CU), patient trained (PT), patient untrained (PU)				
<b>Tasks</b>	<b>Number of, Description of, and Subjective Feedback for Failures/Use Errors, Close Calls and Use Difficulties</b>	<b>Applicant's Root Cause Analysis</b>	<b>Applicant's Discussion of Mitigation Strategies</b>	<b>DMEPA's Analysis and Recommendations</b>
	<p>did not press the plunger far enough to activate the NSD and then pulled needle out of the injection pad. The participant asked if they needed to retract it manually. The participant started to pull back on the plunger but then remembered that they were supposed to press until hearing a click, so they pressed the plunger again activated the NSD.</p>			<p>plunger. In addition, the study investigators observed the full dose being administered; thus, we do not have concern of underdose medication error.</p> <p>Our review of the labels and labeling notes that IFU Step 19 states "Gently release the plunger..." and includes two graphics which depict the deployed NSD. The IFU also states "Slowly inject all of the medicine by gently pushing the plunger all the way down until it touches the activation guards".</p> <p>Based on the overall assessment of the study results and labels and labeling, we find the residual risk acceptable and have no recommendations at this time.</p>

### **ANALYSIS OF NON-CRITICAL TASKS**

We observed use errors/close calls/use difficulties with the following non-critical task:

- Check expiry date

After evaluating the errors pertaining to this use-related task we determined that based on the URRRA this task is not unique to this product. We also determined that due to the non-urgent nature of the proposed product, failure to complete this task will not result in negative clinical impact. Thus, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable.

### **3.4. LABELS AND LABELING**

Tables 3 and 4 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Neurology 2			
	Identified Issue	Rationale for Concern	Recommendation
General Issues			
1.	The non-proprietary name includes a placeholder suffix.	Per the General Advice letter dated March 18, 2020, the proposed suffix -mwge was found conditionally acceptable.	We recommend the nonproprietary name is revised to read “satralizumab-mwge”.

Table 4: Identified Issues and Recommendations for Genentech, Inc			
	Identified Issue	Rationale for Concern	Recommendation
<b>Container Label</b>			
1.	The non-proprietary name includes a placeholder suffix.	Per the General Advice letter dated March 18, 2020, the proposed suffix -mwge was found conditionally acceptable.	We recommend the nonproprietary name is revised to read “satralizumab-mwge”.
2.	As currently presented, the format for the expiration date is not defined.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. <sup>d</sup> FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	The dosage form is not located below the proper name.	For biological products, the finished dosage form can appear on the line below the proper name. <sup>e</sup>	If space permits, consider relocating the dosage form “Injection” so that it appears below the proper name.

<sup>d</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>e</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

4.	The container label does not include the storage information.	Inclusion of the storage information may minimize the risk of deteriorated drug product errors.	If space permits, add “Refrigerate” to the label.
5.	The Rx only statement is too prominent.	The Rx only statement should appear less prominent than other important information on the PDP.	Decrease the prominence of the statement “Rx Only” as this information appears more prominent than the established name on the principal display panel. <sup>f</sup>
6.	It is unclear whether the barcode will be presented vertically.	Barcodes placed in a horizontal position may not scan due to vial curvature. <sup>g</sup>	Ensure the linear barcode is oriented in a vertical position to improve the scannability of the barcode.
<b>Carton Labeling</b>			
1.	Refer to container label recommendations #1-2 and revise accordingly.		
2.	The carton labeling does not include a 2D barcode.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. <sup>h</sup> The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.
3.	The carton labeling does not have a sufficient usual dose statement.	The usual dose statement is required per 21 CFR 201.55.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read “Dosage: See prescribing information.”

<sup>f</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>g</sup> Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

<sup>h</sup> The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>



4.	The storage statement on the back panel can be improved.	Lack of clarity regarding storage conditions might contribute to deteriorated medication errors.	Revise the storage information on the back panel to indicate that “After removing from the refrigerator, may be stored for up to 8 days at a temperature that does not exceed 86°F (30°C) in original carton to protect from light”.
5.	The carton labeling does not inform users that the prefilled syringe should be allowed to warm to room temperature prior to administration.	<p>If users do not refer to the IFU, they may not be aware that after removing the prefilled syringe from refrigeration, the prefilled syringe should be allowed to warm to room temperature prior to administration.</p> <p>If the prefilled syringe does not reach room temperature, there is risk of uncomfortable injection and difficulty administering the product (i.e. make it hard to push the plunger).</p>	Consider including instructions that inform users that the product should be allowed to warm to room temperature prior to administration.

#### **4. CONCLUSION AND RECOMMENDATIONS**

The human factors (HF) validation study results identified use errors, close calls, and use difficulties with critical and non-critical tasks. We did not identify areas of improvement in the proposed user interface based upon review of the subjective feedback from study participants or the root cause analyses. However, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant so that recommendations are implemented prior to approval of this BLA 761149.

##### **4.1 RECOMMENDATIONS FOR THE GENENTECH INC.**

We found the results of your human factors (HF) validation study acceptable. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations for this BLA 761149.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Enspryng that Genentech Inc submitted on November 18, 2019.

<b>Table 5. Relevant Product Information</b>	
<b>Initial Approval Date</b>	N/A
<b>Therapeutic Drug Class or New Drug Class</b>	interleukin-6 (IL-6) receptor antagonist
<b>Active Ingredient (Drug or Biologic)</b>	satralizumab
<b>Indication</b>	(b) (4) for the treatment of adults (b) (4) with neuromyelitis optica spectrum disorder (NMOSD)
<b>Route of Administration</b>	subcutaneous
<b>Dosage Form</b>	injection solution
<b>Strength</b>	120 mg/mL
<b>Dose and Frequency</b>	The recommended loading dose of ENSPRYNG is 120 mg by subcutaneous injection at Weeks 0, 2, and 4 for the first three administrations, followed by a maintenance dose of 120 mg every 4 weeks.
<b>How Supplied</b>	ENSPRYNG (satralizumab) injection is available as a sterile, preservative-free, clear, colorless to slightly yellow solution in single-dose prefilled syringe (PFS) with needle safety device.  ENSPRYNG PFS is not made with natural rubber latex. Each ENSPRYNG carton contains one single-dose 120 mg prefilled syringe (NDC 50242-007-01).
<b>Storage</b>	Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.  Prior to administration, ENSPRYNG, if unopened, can be removed from and returned to the refrigerator, if necessary. If stored at room temperature, the total combined time out of refrigeration should not exceed 8 days at a temperature that does not exceed 30°C

<b>Container Closure/Device Constituent</b>	<div>(b) (4)</div>
<b>Intended Users</b>	HCP, caregivers, patients
<b>Intended Use Environment</b>	Home, clinical

## **APPENDIX B. BACKGROUND INFORMATION**

### **B.1 PREVIOUS HF REVIEWS**

#### **B.1.1 Methods**

On February 20, 2020, we searched the L:drive and AIMS using the terms, satralizumab and IND 118183, to identify reviews previously performed by DMEPA or CDRH.

#### **B.1.2 Results**

Our search identified one previous review<sup>i</sup>, and we confirmed that our previous recommendations were either implemented or considered.

## **APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS**

The background information can be accessed in EDR via:

<\\cdsesub1\evsprod\bla761149\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ngo\5354-other-stud-rep\human-factors-engineering-summary-report\att-pfs-hfvs-ig.pdf>

## **APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT**

The HF study results report can be accessed in EDR via:

<\\cdsesub1\evsprod\bla761149\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ngo\5354-other-stud-rep\human-factors-engineering-summary-report\hfes-report-body.pdf>

## **APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW**

On August 12, 2019, the Agency sent an Information Request (IR) to the Applicant to request clarification regarding the HF study participant characteristics and dosing regimen. The IR also requested product samples. The Applicant responded to the IR on August 16, 2019. See EDR link: <\\cdsesub1\evsprod\bla761149\0005\m1\us\20190916-quality-ir.pdf>

On October 28, 2019, the Agency sent an IR to the Applicant to request additional details regarding participant performance during the HF validation study and to request the moderator's script. The Applicant responded to the IR on November 18, 2019. See EDR link: <\\cdsesub1\evsprod\bla761149\0014\m1\us\20191118-rtoq.pdf>

On January 14, 2020, the Agency sent an IR to the Applicant requesting justification for the education demographics of the participants in the HF validation study. The Applicant responded to the IR on January 21, 2020. See EDR link: <\\cdsesub1\evsprod\bla761149\0019\m1\us\20200121-ir-qual-resp.pdf>

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<sup>i</sup> Rider, B. Human Factors Protocol Review for SA237 (sapelizumab) injection IND 118183. Silver Spring (MD): FDA, CDR, OSE, DMEPA (US); 2017 MAY 19. RCM No.: 2017-438.

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>j</sup> along with postmarket medication error data, we reviewed the following Enspryng labels and labeling submitted by Genentech Inc.

- Container label received on August 15, 2019
- Carton labeling received on August 15, 2019
- Instructions for Use (Image not shown) received on August 15, 2019
  - <\\cdsesub1\evsprod\bla761149\0004\m1\us\ifu.pdf>
- Prescribing Information (Image not shown) received on December 4, 2019
  - <\\cdsesub1\evsprod\bla761149\0015\m1\us\draft-labeling-text.pdf>

### F.2 Label and Labeling Images

#### Container label



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<sup>j</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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EBONY A WHALEY  
04/28/2020 11:36:32 AM

LOLITA G WHITE  
04/28/2020 05:51:01 PM

QUYNHNHU T NGUYEN  
04/29/2020 01:30:57 PM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS  
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	4/16/2020		
To:	Oumou Barry		
Requesting Center/Office	CDER/OPQ	Clinical Review Division	Choose an item.
From	Rong Guo OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Devices Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR: ICCR# 00012224 ICC: ICC1900699 Submission: BLA 761149 Sponsor: GENENTECH INC Biologic: Enspryng (satralixumab) Indications for Use: Satralizumab is indicated in adults (b) (4) for the treatment of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD).		
Recommendation	<b>Final Recommendation:</b> <input checked="" type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable. <input type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, <input type="checkbox"/> Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies <b>Comments to Review Team:</b> n/a <b>PMC/PMR or CR Deficiencies:</b> n/a		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Rong Guo -S <small>Digitally signed by Rong Guo -S            DN: c=US, o=U.S. Government, ou=HHS,            ou=FDA, ou=People, cn=Rong Guo -S,            0.9.2342.19200300.100.1.1=2000718961            Date: 2020.04.16 15:18:19 -04'00'</small>	Rumi Young -S <small>Rumi Young -S            c=US, o=U.S. Government, ou=HHS,            ou=FDA, ou=People, cn=Rumi            Young -S,            0.9.2342.19200300.100.1.1=2002467            913            2020.04.17 08:23:00 -04'00'</small>	



# 1. PURPOSE

This review provides an assessment of the syringe device constituent part of the prefilled syringe product.

This review will cover the following review areas:

- ☒ Device performance
- ☒ Stability – device performance on stability
- ☒ Essential Performance Requirements (EPR) Control strategy

## ☒ CDRH Quality Systems Assessment / Facilities consult not required

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential<sup>1</sup>) treatment that are administered by non-health care professionals.

# 2. DEVICE DESCRIPTION

## 2.1. Picture of Final Device Presentation

The primary packaging components used for the manufacture of satralizumab 120 mg/mL prefilled syringe (PFS) for subcutaneous administration consist of a 1 mL colorless USP/Ph. Eur./JP compliant (b) (4) syringe with a staked-in, stainless steel needle, fitted with a (b) (4) needle shield and sealed with a (b) (4) plunger stopper.

**Table P.7-1 Primary Container Closure Description**

Reference to Figure	Components	Description	Sterilization Method	Supplier	DMF Number
A	Staked-in needle syringe	1 mL, long syringe, colorless (b) (4) barrel, 27G 1/2", thin wall, stainless steel needle. The (b) (4)			(b) (4)
		stainless steel needle (A1) (b) (4)			
B	Rigid needle shield (RNS)				
C	Plunger stopper				

<sup>a</sup> Refer to Attachment P.7 Letter of Authorization—(b) (4)Syringe.

<sup>b</sup> Refer to Attachment P.7 Letter of Authorization—Plunger Stopper.

The device constituent part of the combination product is the assembled PFS which includes the PFS, needle safety device (NSD), and extended finger flange (EFF).

<sup>1</sup> Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

**Figure R.3-2**

**Components of the Satralizumab Assembled PFS**



The device components are 510(k) cleared medical devices manufactured by (b) (4) as listed below:



**2.2. Design Requirements**

**Syringe Description**

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	HCP and adult patient self-administration
Injection Site	sites in the abdomen or thigh, and should be rotated with each injection.
Injection tissue and depth of injection	subcutaneous use only
Needle connection (e.g. luer, slip tip, staked)	Staked
Syringe Volume	1 mL
Delivered Dose Volume	≥ 1.0 mL

**Additional Devices**

Requirement	Describe
Hypodermic Needle: (length, gauge)	27 G, 1/2"

Safety Features (e.g. Needle safety component/device)	(b) (4)
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### 3. DEVICE PERFORMANCE REVIEW

Performance Requirement	Specification	Verification Method <b>Acceptable</b> (Y/N)	Validation (Y/N)	Stability Module 3.2.P.8 (Y/N)	Shipping/Transportation (Y/N)
Dose Accuracy	$\geq 1.0$ mL	Y	Y	Y	Y
Break loose Force on PFS	(b) (4) N	Y	Y	Y	Y
Average Injection Force on PFS	(b) (4) N	Y	Y	Y	Y
Peak Force on assembled PFS	(b) (4) N	Y	Y		
Cap Removal Force	(b) (4) N	Y		n/a	n/a
Needle Safety Device Performance	NSD override force (b) (4) N	Y		n/a	n/a

**Table R.3-9 Design Verification Testing Results Summary**

Verification Test	Acceptance Criterion for Design Verification	Result (T0)
CCI	(b) (4) mbar $\times$ L/s	Pass
RNS Removal Force	(b) (4) N	Pass
Average Injection Force	N	Pass
Peak Force	N	Pass
Deliverable Volume	$\geq 1.0$ mL	Pass
NSD Override Force	(b) (4) N	Pass
Integrity After Drop Test Testing	Assembled PFS must be integral (defect free, no damages)	Pass
Needle Pull Out Force	(b) (4) N	Pass

**Table R.3-11 Results 36-month Accelerated Aging**

Functionality Test Parameters													
Time (months)	CCI Pass/Fail	RNS Removal Force Pass/Fail	Average Injection Force Pass/Fail			Peak Force Pass/Fail			Deliverable Volume Pass/Fail			NSD Override Force Pass/Fail	Drop Test Pass/Fail
Batch	17D020E	T7K03	17D010E	17D020E	17E010E	17D010E	17D020E	17E010E	17D010E	17D020E	17E010E	T7K03	T7K03
Sample Size	119	26	26	26	26	26	26	26	19	19	19	26	19
0	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
3	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
6	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
9	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

Note 1: For device functionality, the acceleration factor is assumed to be 4 (using the Arrhenius equation). For example, 9 months under accelerated conditions equals 36-month real time.

**Table R.3-10 Results Real-Time Aging (design verification batches) (cont.)**

Functionality Test Parameters														
Time (months)	CCI Pass/Fail	RNS Removal Force Pass/Fail	Average Injection Force Pass/Fail			Peak Force Pass/Fail			Deliverable Volume Pass/Fail			NSD Override Force Pass/Fail	Drop Test Pass/Fail	Needle Pull Out Force Pass/Fail
Batch	17D020E	T7K03	17D010E	17D020E	17E010E	17D010E	17D020E	17E010E	17D010E	17D020E	17E010E	T7K03	T7K03	T7K03
6	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	NT	Pass
9	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	NT	Pass
12	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	NT	Pass
18	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	NT	Pass
24	Pending	Pending	Pending			Pending			Pending			Pending	NT	Pending
30	Pending	Pending	Pending			Pending			Pending			Pending	NT	Pending
36	Pending	Pending	Pending			Pending			Pending			Pending	NT	Pending

Abbreviation: NT = not tested, as per internal protocol (based on expert review, aging is not influencing this functionality test parameter).

An IR was sent to the Sponsor on 01/16/2020:

1. In 3.2. R Medical Device, you provided a brief summary of the design verification of the device EPRs. However, without the reports, we cannot determine whether the device EPRs are adequately verified. Provide the design verification reports and ensure they include the following: sample size, mean, max, min, K-value (if applicable), standard deviation, confidence/reliability targets, graphical summary and summary of deviations (if any).

Sponsor responded on 02/12/2020 and provided reports in “2020-02-12\_ Response to Questions Raised by FDA issued on 16 January 2020”. The following are the summaries.

#### Dose accuracy

The Design Input Requirement (DIR) for the Deliverable Volume is  $V \geq 1.0$  mL with an acceptance criterion of V (b) (4) ml with k-value (b) (4). The test results for the different time-points are listed in Table 5 below.

Table 5: Deliverable Volume data [mL]

		T0		Real Time Aging							
		w/o sh	w sh	T3	T6	T9	T12	T18	T24	T36	T48
DV 1, 17D010E	mean	N/A	1.0338	1.0305	1.0359	1.0303	1.0349	1.0392	1.0403	— *	— *
	s	N/A	0.0035	0.0109	0.0061	0.0038	0.0049	0.0053	0.0082	— *	— *
	min	N/A	1.0248	0.9903	1.0250	1.0221	1.0251	1.0295	1.0248	— *	— *
	max	N/A	1.0404	1.0446	1.0480	1.0383	1.0426	1.0487	1.0542	— *	— *
DV 2, 17D020E	mean	N/A	1.0369	1.0363	1.0403	1.0304	1.0361	1.0384	1.0442	— *	— *
	s	N/A	0.0060	0.0064	0.0076	0.0077	0.0064	0.0052	0.0077	— *	— *
	min	N/A	1.0213	1.0231	1.0232	1.0155	1.0257	1.0281	1.0259	— *	— *
	max	N/A	1.0462	1.0453	1.0494	1.0412	1.0478	1.0456	1.0559	— *	— *
DV 3, 17E010E	mean	N/A	1.0367	1.0360	1.0334	1.0341	1.0358	1.0364	1.0411	— *	— *
	s	N/A	0.0063	0.0051	0.0053	0.0052	0.0041	0.0058	0.0082	— *	— *
	min	N/A	1.0252	1.0263	1.0216	1.0233	1.0298	1.0270	1.0289	— *	— *
	max	N/A	1.0452	1.0445	1.0403	1.0426	1.0446	1.0500	1.0545	— *	— *

\* data not yet available

T0:  $k_{\text{calculated}} = 23.870$  (DV1), 14.360 (DV2) and 13.694 (DV3)  $\geq k_{\text{target}} =$  (b) (4)

! T3:  $k_{\text{calculated}} = 2.477^*$  (DV1), 13.511 (DV2) and 16.878 (DV3)  $\geq k_{\text{target}} =$  (b) (4)  
! T6:  $k_{\text{calculated}} = 13.992$  (DV1), 11.854 (DV2) and 15.693 (DV3)  $\geq k_{\text{target}} =$   
! T9:  $k_{\text{calculated}} = 21.269$  (DV1), 10.392 (DV2) and 16.100 (DV3)  $\geq k_{\text{target}} =$   
! T12:  $k_{\text{calculated}} = 17.203$  (DV1), 13.409 (DV2) and 20.743 (DV3)  $\geq k_{\text{target}} =$   
! T18:  $k_{\text{calculated}} = 16.983$  (DV1), 16.848 (DV2) and 15.011 (DV3)  $\geq k_{\text{target}} =$   
! T24:  $k_{\text{calculated}} = 10.994$  (DV1), 12.204 (DV2) and 11.115 (DV3)  $\geq k_{\text{target}} =$

\* The k-value is calculated after transformation

**Peak forces**

The Design Input Requirement (DIR) for the Peak Force is  $F =$  (b) (4) N with an additional acceptance criterion of k-value (b) (4)  
(b) (4) The test results for the different time-points are listed in Table 6 below.

Table 6: Peak Force data [N]

		T0		Real Time Aging							
		w/o sh	w sh	T3	T6	T9	T12	T18	T24	T36	T48
DV 1, 17D010E	mean	8.9	9.2	9.3	10.1	9.5	10.1	10.2	11.0	— *	— *
	s	0.5	0.6	0.7	1.2	1.0	1.2	0.8	1.1	— *	— *
	min	8.2	8.0	8.1	8.6	8.3	8.2	8.9	9.0	— *	— *
	max	10.1	10.5	11.6	13.5	13.4	13.6	11.8	13.0	— *	— *
DV 2, 17D020E	mean	8.8	9.9	10.2	9.3	9.5	9.4	11.9	11.6	— *	— *
	s	0.6	0.8	1.6	0.7	0.6	0.9	1.9	1.4	— *	— *
	min	8.1	8.3	8.6	8.3	9.0	8.1	9.5	9.2	— *	— *
	max	10.4	11.3	15.8	11.2	11.0	11.6	17.0	14.3	— *	— *
DV 3, 17E010E	mean	9.0	9.8	10.1	10.8	10.3	10.0	13.3	14.5	— *	— *
	s	0.5	0.7	1.3	1.3	1.3	1.0	1.1	2.7	— *	— *
	min	8.2	8.6	8.4	8.1	9.1	8.6	11.2	9.6	— *	— *
	max	10.0	11.7	14.2	13.4	14.4	13.0	15.4	21.8	— *	— *

\* data not yet available

T0:

Without shipping simulation:

!  $k_{\text{calculated}} = 50.629$  (DV1), 5.105\* (DV2) and 52.922 (DV3)  $\geq k_{\text{target}} =$  (b) (4)

With shipping simulation:

!  $k_{\text{calculated}} = 39.594$  (DV1), 29.997 (DV2) and 4.517\* (DV3)  $\geq k_{\text{target}} =$  (b) (4)T3:  $k_{\text{calculated}} = 32.012$  (DV1), 2.999\* (DV2) and infinite\* (DV3)  $\geq k_{\text{target}} =$  (b) (4)T6:  $k_{\text{calculated}} = 18.728$  (DV1), 32.133 (DV2) and 17.374 (DV3)  $\geq k_{\text{target}} =$ T9:  $k_{\text{calculated}} = 3.797^*$  (DV1), infinite\* (DV2) and infinite\* (DV3)  $\geq k_{\text{target}} =$ T12:  $k_{\text{calculated}} = 19.147$  (DV1), 27.271 (DV2) and 5.529\* (DV3)  $\geq k_{\text{target}} =$ T18:  $k_{\text{calculated}} = 28.546$  (DV1), infinite\* (DV2) and 17.212 (DV3)  $\geq k_{\text{target}} =$ T24:  $k_{\text{calculated}} = 19.990$  (DV1), 15.141 (DV2) and 6.798 (DV3)  $\geq k_{\text{target}} =$

### Average injection forces

The Design Input Requirement (DIR) for the Average Injection Force is  $F_{(b)(4)} N$  with an additional acceptance criterion of k-value  $(b)(4)$ . The test results for the different time-points are listed in Table 7 below.

Table 7: Average Injection Force data [N]

		T0		Real Time Aging							
		w/o sh	w sh	T3	T6	T9	T12	T18	T24	T36	T48
DV 1, 17D010E	mean	3.6	3.6	3.5	3.5	3.5	3.5	3.6	3.5	— *	— *
	s	0.2	0.2	0.1	0.1	0.2	0.2	0.2	0.1	— *	— *
	min	3.3	3.2	3.2	3.2	3.2	3.2	3.4	3.3	— *	— *
	max	4.0	4.2	3.8	3.8	4.0	3.8	4.0	3.7	— *	— *
DV 2, 17D020E	mean	3.5	3.7	3.9	3.6	3.6	3.6	3.8	3.7	— *	— *
	s	0.1	0.2	0.3	0.1	0.1	0.2	0.3	0.2	— *	— *
	min	3.3	3.3	3.5	3.4	3.3	3.4	3.4	3.3	— *	— *
	max	3.9	4.3	4.5	3.8	3.9	3.9	4.2	4.0	— *	— *
DV 3, 17E010E	mean	3.5	3.5	3.5	3.5	3.6	3.5	3.7	3.7	— *	— *
	s	0.1	0.2	0.2	0.1	0.2	0.1	0.2	0.3	— *	— *
	min	3.2	3.3	3.3	3.4	3.4	3.4	3.3	3.4	— *	— *
	max	3.7	3.9	4.1	3.9	4.6	3.8	4.1	4.4	— *	— *

\* data not yet available

T0:

Without shipping simulation:

$$! \quad k_{\text{calculated}} = 117.342 \text{ (DV1)}, 6.964^* \text{ (DV2)} \text{ and } 4.622^* \text{ (DV3)} \geq k_{\text{target}} = (b)(4)$$

With shipping simulation:

$$! \quad k_{\text{calculated}} = 112.079 \text{ (DV1)}, 4.592^* \text{ (DV2)} \text{ and } 5.629^* \text{ (DV3)} \geq k_{\text{target}} = (b)(4)$$

$$T3: k_{\text{calculated}} = 182.786 \text{ (DV1)}, 5.021^* \text{ (DV2)} \text{ and } 5.153^* \text{ (DV3)} \geq k_{\text{target}} = (b)(4)$$

$$T6: k_{\text{calculated}} = 155.453 \text{ (DV1)}, 261.193 \text{ (DV2)} \text{ and } 196.706 \text{ (DV3)} \geq k_{\text{target}} = (b)(4)$$

$$T9: k_{\text{calculated}} = 134.367 \text{ (DV1)}, 164.982 \text{ (DV2)} \text{ and } \text{infinite}^* \text{ (DV3)} \geq k_{\text{target}} =$$

$$T12: k_{\text{calculated}} = 145.986 \text{ (DV1)}, 146.988 \text{ (DV2)} \text{ and } 7.274^* \text{ (DV3)} \geq k_{\text{target}} =$$

$$T18: k_{\text{calculated}} = \text{infinite}^* \text{ (DV1)}, 77.945 \text{ (DV2)} \text{ and } 112.398 \text{ (DV3)} \geq k_{\text{target}} =$$

$$T24: k_{\text{calculated}} = 206.567 \text{ (DV1)}, 129.212 \text{ (DV2)} \text{ and } 5.222^* \text{ (DV3)} \geq k_{\text{target}} =$$

### Needle Pull Out Force

The Design Input Requirement (DIR) for the Needle Pull Out Force  $F_{(b)(4)} N$  with an additional acceptance criterion of k-value  $(b)(4)$ . The test results for the different time-points are listed in Table 8.

Table 8: Needle Pull Out Force data [N]

T0			Real Time Aging							
	w/o sh	w sh	T3	T6	T9	T12	T18	T24	T36	T48
mean	N/A	101.5	100.7	102.3	102.6	101.9	100.3	101.2	— *	— *
s	N/A	4.3	3.3	4.0	3.5	3.7	4.3	4.1	— *	— *
min	N/A	95.2	94.8	96.5	97.3	94.6	89.6	92.9	— *	— *
max	N/A	106.8	106.4	110.5	109.3	107.9	106.2	107.8	— *	— *

\* data not yet available

$$T0: k_{\text{calculated}} = \text{infinite}^* \geq k_{\text{target}} = (b)(4)$$

$$T3: k_{\text{calculated}} = 23.565 \geq k_{\text{target}} =$$

$$T6: k_{\text{calculated}} = 20.039 \geq k_{\text{target}} =$$

$$T9: k_{\text{calculated}} = \text{infinite}^* \geq k_{\text{target}} =$$

$$T12: k_{\text{calculated}} = 21.806 \geq k_{\text{target}} =$$

$$T18: k_{\text{calculated}} = 18.287 \geq k_{\text{target}} =$$

$$T24: k_{\text{calculated}} = 19.451 \geq k_{\text{target}} =$$

### NSD Override force

The Design Input Requirement (DIR) for the NSD Override force is  $F_{(b)(4)} N$  with an additional acceptance criterion of k-value  $(b)(4)$ . The test results for the different time-points are listed in Table 9.



Table 9: NSD Override force data data

	T0		Real Time Aging							
	w/o sh	w sh	T3	T6	T9	T12	T18	T24	T36	T48
mean	N/A	137.3	138.7	133.6	134.7	135.6	134.7	133.7	— *	— *
s	N/A	4.5	4.4	3.9	5.5	2.7	3.9	3.9	— *	— *
min	N/A	128.7	132.6	130.0	126.8	128.4	129.2	128.1	— *	— *
max	N/A	150.5	150.3	146.0	145.7	142.5	148.4	142.4	— *	— *

\* data not yet available

T0:  $k_{\text{calculated}} = 14.462 \geq k_{\text{target}} = (b) (4)$

! T3:  $k_{\text{calculated}} = 15.090 \geq k_{\text{target}} = (b) (4)$

! T6:  $k_{\text{calculated}} = 16.554 \geq k_{\text{target}} =$

! T9:  $k_{\text{calculated}} = 11.412 \geq k_{\text{target}} =$

! T12:  $k_{\text{calculated}} = 23.281 \geq k_{\text{target}} =$

! T18:  $k_{\text{calculated}} = 12.118^* \geq k_{\text{target}} =$

! T24:  $k_{\text{calculated}} = 9.881^* \geq k_{\text{target}} =$

\* The k-value is calculated after transformation

An IR was sent on 04/10/2020:

*In our IR sent on 1/16/2020, we asked for design verification reports and ensure they include the following: sample size, mean, max, min, K-value (if applicable), standard deviation, confidence/reliability targets, graphical summary and summary of deviations (if any). However, your response on 2/12/2020 does not specify the sample size and confidence/reliability targets. In addition, your provided  $K_{\text{target}}$  value (b) (4). Please provide a table summary outlining the sample size,  $K_{\text{target}}$  value, and confidence/reliability targets for the following attributes: Peak force, Break loose force, Average injection force, Deliverable volume, and NSD Override force. Please note per FDA Guidance for Industry and FDA Staff “Medical Devices with Sharps Injury Prevention Features”, we expect a 99% reliability limit for NSD override force testing based of the associated safety concerns.*

Sponsor responded with the following table:

**Table 1 Statistical data for requested SA237 PFS-NSD design verification attributes**

Design Attribute	Sample Size (variable sampling) (per time point) <sup>a</sup>	target K value	Probability (%) confidence target / % reliability target) <sup>c</sup>	Design Verification outcome
Peak Force (including Break Loose Force <sup>b</sup> )	26	(b) (4)	(b) (4)	Pass
Average Injection Force	26			Pass
Deliverable Volume	19			Pass
NSD Override Force	26			Pass

<sup>a</sup> Sample Size, number tested per batch and time point.

<sup>b</sup> As explained in IR8 (response to questions raised by FDA issued 01/16/2020), Break loose force is a component of Peak Force and not a separate design input requirement (DIR). Therefore, Break loose force has under gone design verification only as part of the DIR Peak Force.

<sup>c</sup> no failure allowed (c=0) for all sampling plans.

An IR was sent on 04/13/2020:

## Clinical Inspection Summary

<b>Date</b>	4/6/2020
<b>From</b>	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Susan Daugherty, Regulatory Project Manager Lawrence Rodichok, M.D., Medical Officer Division of Neurology 2 Office of Neuroscience
<b>BLA#</b>	761149
<b>Applicant</b>	Genentech, Inc.
<b>Drug</b>	Satralizumab
<b>NME</b>	Yes
<b>Proposed Indication</b>	Treatment of neuromyelitis optica and neuromyelitis optica spectrum disorders
<b>Consultation Request Date</b>	10/9/2019
<b>Summary Goal Date</b>	4/15/2020
<b>Priority/Standard Review</b>	Standard
<b>Action Goal Date</b>	8/15/2020
<b>PDUFA Date</b>	8/15/2020

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Eubank and Javed were inspected in support of this NDA and covered Protocol BN40900 (SA-309JG). The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

One issue was identified at Dr. Eubank's site. Subject (b) (6) randomized to satralizumab, withdrew consent approximately one month prior to experiencing a protocol-defined neuromyelitis optica spectrum disorder (NMOSD) relapse but was included in the primary efficacy analysis. Although we note this was an isolated finding, we recommended that the review division conduct a sensitivity analysis excluding this subject.

(b) (4)



## II. BACKGROUND

Satralizumab for subcutaneous injection is being developed by Genentech, Inc. under BLA 761149 (IND 118183) for the treatment of neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD). The IND was transferred from Chugai Pharma USA, Inc. to Genentech, Inc., in April 2019. Chugai Pharma was the sponsor when the clinical studies were conducted.

The sponsor has submitted two Phase 3 studies, BN40898 (SA-307JG, an add-on study) and BN40900 (SA-309JG, a monotherapy study) to support the efficacy and safety of satralizumab in the treatment of NMO and NMOSD. Clinical inspections were requested only for Protocol BN40900, the monotherapy study.

### Protocol BN40900 (SA-309JG, SAkuraStar)

*Title:* “A multicenter, randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of satralizumab as monotherapy in patients with neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD)”

*Subjects:* 95

*Sites:* 44 sites in North America (United States 20, Canada 3), Eastern Europe (13), Asia/Pacific (5), Middle East/Central Asia (2), and Western Europe (1)

*Study Initiation and Completion Dates:* 8/5/2014 – 10/12/2018 (data cut-off)

This was a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of satralizumab as monotherapy in subjects with neuromyelitis optica (NMO) or NMO spectrum disorder (NMOSD). Enrolled were male or female subjects, 18 to 74 years of age, with a diagnosis of NMO or NMOSD, seropositive or seronegative for anti-AQP4 antibody ( $\leq 30\%$  of adult subjects could be seronegative), clinical evidence of at least one documented relapse in the last 12 months prior to screening, and Expanded Disability Status Scale (EDSS) score 0 to 6.5 (inclusive) at screening. Subjects were excluded if they had a clinical relapse onset (including first attack) within 30 days prior to baseline.

The study consisted of four phases:

**Screening** – 28 days

**Double-Blind Phase** – lasting until the clinical cut-off date (CCOD) of 10/12/2018 (see below)

Subjects were randomized (2:1) to one of two treatment groups:

- Satralizumab 120 mg subcutaneous (SC) injection at Weeks 0, 2, 4, and every 4 weeks thereafter or

- Placebo SC injection at Weeks 0, 2, 4, and every 4 weeks thereafter

Randomization was stratified by baseline therapy (B-cell depleting therapy or immunosuppressants/other) and the most recent relapse (first attack or relapse) in the last year prior to screening.

**Safety Follow-up** – lasting until 24 weeks from the last dose of investigational product. Subjects who withdrew from the double-blind phase due to a clinical relapse were asked to participate in the safety follow-up phase. A telephone interview was to be conducted by site personnel every 4 weeks from last investigational product dosing to identify any new or worsening neurological symptoms.

**Open Label Extension** – lasting until commercial availability of satralizumab (at least 96 weeks)

Subjects who completed the double-blind phase or experienced a protocol-defined relapse (see below) in the double-blind phase could enter the open-label extension. Satralizumab 120 mg SC injection was administered at Weeks 0, 2, 4, and every 4 weeks thereafter

An independent data monitoring committee (DMC) was established to monitor safety and study conduct in the double-blind phase of the study. The DMC periodically reviewed unblinded by-treatment group safety and key efficacy summaries prepared by an independent data coordinating center.

During the double-blind phase, subjects were to report to the site all new or worsening neurological signs and symptoms compatible with NMO and NMOSD that were suggestive of a relapse. The blinded examining investigator performed an EDSS/FSS assessment within 7 days to confirm whether a relapse had occurred or not. Any relapse reported by the investigator was considered as a *clinical* relapse. A *protocol-defined* relapse was a clinical relapse that was confirmed to be a protocol-defined relapse by the Clinical Endpoint Committee (CEC). The CEC adjudicated all investigator-reported relapses in a blinded manner to confirm whether the relapse met criteria for a protocol-defined relapse.

In the original protocol (2/18/2014), the end of the double-blind period (clinical cut-off date, CCOD) was defined as the date when the total number of relapses reached 19, which was estimated to take approximately 27 months from the time the first subject was enrolled. Amendment 6 (3/1/2016) changed the CCOD definition to the date when the total number of relapses reached 44; the double-blind phase was estimated to last approximately 38 months to reach this number of relapses. Amendment 8 (6/14/2018) changed the CCOD to the date when the total number of relapses reached 44 or 1.5 years after the date of randomization of the last subject enrolled, whichever came first. The CCOD for protocol amendment 8 occurred on 10/12/2018, 1.5 years after the date of randomization of the last subject enrolled.

The **primary efficacy endpoint** was the time to first relapse based on CEC-confirmed protocol-defined relapse during the double-blind period.

Potential Unblinding Issue

In October 2017, Chugai Pharmaceutical Co., Ltd/Japan, the sponsor at the time the clinical trials were conducted, contacted the review division to discuss a potential unblinding issue identified for Protocols SA-307JG and SA-309JG. In these clinical trials, fibrinogen levels were routinely obtained, and the unblinded results were available to both Chugai and treating investigators. In June 2017, several Chugai team members located in the Japan office allegedly attempted to determine treatment assignment in these clinical trials based on the change in fibrinogen levels. Decreases in fibrinogen levels associated with the study drug have been found in prior studies and is described in the Clinical Investigator Brochure. The changes in fibrinogen levels were reportedly used to assume treatment assignments of subjects, draw Kaplan-Meier curves, and calculate hazard ratios for the primary endpoint. An initial investigation by Chugai and Roche was conducted in or around July 2017. Of note, F. Hoffman La-Roche was responsible for statistical programming and analysis as well medical writing for these protocols.

During the investigation, it was found that treatment assignment assumptions were made on two separate occasions, in November 2015 and June 2017. Corrective and preventive actions were instituted and included limiting efficacy reviewer access to laboratory parameters, removing team members involved in the analysis from the protocols, retraining of all Chugai personnel regarding blinding procedures, performing an independent audit by an external party, and analysis of potential biases on the clinical data.

The results of the independent audit, conducted by (b) (4) on December 13-15, 2017, was submitted to IND 118183 on February 6, 2018. The purpose of this audit was to verify Chugai's corporate internal GCP compliance activities regarding the treatment assignment assumption findings. The audit covered Chugai's organizational structure and interviews with key personnel, documentation related to the treatment assignment assumption, Corrective and Preventive Action (CAPA) processes that had been initiated to address the events, clinical operations including adherence to Standard Operating Procedures (SOPs), quality management system as related to the treatment assignment assumption, and regulatory documentation including correspondence with FDA. This audit identified four major findings and no critical findings. Briefly, these findings included:

- SOPs to address the dissemination and reporting of treatment assignment assumption information were inadequately adhered to
- A lack of SOPs to guard against inappropriate dissemination of treatment assignment assumption
- Inadequate CAPA processes for several items including a lack of corrective action to be taken for biostatisticians
- Delinquencies in reporting of the events to Quality Assurance personnel

Recommendations from the audit included creating/revising SOPs, providing additional documentation of actions taken in response to the events, creating a communication plan between Chugai and Roche, and providing greater detail for the CAPAs taken by Chugai so as

to limit any impact on the final analysis and to ensure that the treatment assignment assumption events are not repeated.

The Good Clinical Practice Oversight Branch (GCOB) of OSI was involved in reviewing the results of the independent audit report and providing feedback to the review division. GCOB determined that the issues identified in the audit did not appear to represent issues of compliance. GCOB recommended that an inspection of Chugai be conducted when the BLA was submitted.

IND 118183, under which these clinical trials were conducted, was transferred from Chugai to Genentech, Inc. (a member of the Roche family) effective April 1, 2019. BLA 761149 (part 1, rolling submission) was submitted on June 27, 2019 identifying the applicant as Genentech, Inc.

A bias assessment report regarding treatment assignment assumption incidents was included in the BLA submission. The sponsor assessed three potential sources of bias including sponsor bias on treatment assignment assumptions from inpatient changes in fibrinogen test results, subsequent calculation of primary endpoint hazard ratios, and Protocol BN40900 protocol amendments; study management team bias based on access to the fibrinogen results; and treating investigator bias based on access to the fibrinogen results. The sponsor stated that, overall, no evidence of bias resulting from the availability of fibrinogen test results was identified at the sponsor or treating investigator level.

(b) (4)

### **Rationale for Site Selection**

The clinical sites were chosen primarily based on numbers of enrolled subjects at US sites, number of relapse events at the site to evaluate, and prior inspectional history.

## **III. RESULTS**

### **1. Geoffrey Alan Eubank, M.D.**

Site #2541

OhioHealth Neurological Physicians

931 Chatham Lane

Columbus, OH 43221

Inspection Dates 12/3/2019 – 12/10/2019

At this site for Protocol BN40900 (SA-309JG), 4 subjects were screened, 3 subjects were randomized and completed the double-blind phase, and 2 subjects are currently in the open-label extension phase. One subject withdrew consent (see below).

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 efficacy endpoint data (date of NMO/NMOSD protocol-defined relapse, EDSS scores).

Subjects (b) (6) and (b) (6) experienced protocol-defined NMOSD relapses. The date for these attacks were verified during the inspection. Consistent with the protocol, EDSS/FSS assessments were completed within 7 days of the subject reporting relapse symptoms to the site. EDSS scores were recorded on paper case report forms. The FDA field investigator verified the EDSS scores against the sponsor data line listings; no discrepancies were identified.

Subject (b) (6) randomized to satralizumab, withdrew consent on (b) (6) as she was considering pregnancy and different treatment options. Her last dose of satralizumab was on (b) (6). According to the protocol, for subjects withdrawing from the study, “every effort should be made to conduct the visit (withdrawal visit) at 12 weeks after the last dosing.” On (b) (6) the subject contacted the site to report relapse symptoms. The relapse visit occurred on (b) (6). The subject’s withdrawal visit occurred on (b) (6). Although the subject had withdrawn consent on (b) (6) the sponsor’s disposition listings state that consent was withdrawn on (b) (6) the date of the withdrawal visit. This subject’s CRF confirms that consent was withdrawn on (b) (6).

There was no evidence of underreporting of adverse events. Two subjects experienced SAEs at this site:

- Subject (b) (6) – intracranial aneurysm (preexisting, aneurysm growth), occurred during open-label phase
- Subject (b) (6) – pulmonary sepsis, occurred during double-blind phase (randomized to satralizumab)

Consistent with the protocol, SAEs were reported to the sponsor and IRB within 24 hours of the study staff’s awareness of the events. Narratives for these SAEs are included in the BLA submission.

*Reviewer’s comment: Subject (b) (6) withdrew consent from the study prior to experiencing an NMOSD relapse and should not, therefore, be included in the primary efficacy analysis. We recommended that the review division perform a sensitivity analysis excluding this subject.*

*Since this subject withdrew consent and stopped taking investigational product prior to the relapse, there was a time gap in the exposure (EX.JMP) and clinical events (CE.JMP) datasets. This reviewer examined these datasets and did not identify any other instances of subjects with time gaps between investigational product administration and relapse.*

**2. Adil Javed, M.D.**

Site #2515

5841 S. Maryland Avenue

Chicago, IL 60637

Inspection Dates 10/31/2019 – 11/6/2019

At this site for Protocol BN40900 (SA-309JG), 6 subjects were screened, 5 subjects were randomized and completed the double-blind phase, and 3 subjects are currently in the open-label extension phase. One subject withdrew consent during the open-label phase and another subject continued in the open-label phase but was transferred to a different clinical site (Site #2512/Florida) with approval from the sponsor.

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 efficacy endpoint data (date of NMO/NMOSD protocol-defined relapse, EDSS scores).

Subject (b) (6) randomized to satralizumab, experienced a protocol-defined NMOSD relapse. The date for the attack was verified during the inspection. Consistent with the protocol, EDSS assessments were completed within 7 days of the subject reporting relapse symptoms to the site. EDSS scores were recorded on paper case report forms. The FDA field investigator verified the EDSS scores against the sponsor data line listings; no discrepancies were identified.

The baseline EDSS assessment for Subject (b) (6) was conducted on (b) (6) and this subject experienced a protocol-defined NMOSD relapse beginning on (b) (6). The subject informed the site of relapse symptoms on (b) (6) and an EDSS assessment was performed on (b) (6). The CRO, (b) (4) emailed the site (b) (6) (approximately 1 week after the date of the relapse EDSS assessment) stating that the (b) (4) medical monitor had raised some queries regarding Relapse Assessment Form data and EDSS scores for both the baseline and relapse assessments. Based on these queries, which the clinical investigator and another EDSS investigator deemed to be “clerical” in nature (according to a memo-to-file), changes were made to the baseline EDSS score. The baseline EDSS score was changed from EDSS step 4 to 4.5 (i.e., pyramidal changed from 3 to 4, sensory changed from 1 to 3). The EDSS score for the relapse was 5.5 and was not changed.

According to the study delegation log, there were four sub-investigators who were assigned the task of EDSS assessment throughout the course of the study. For three of these sub-investigators, it appears that they were initially (11/2014) assigned a variety of study-related tasks (e.g., adverse event interpretation, SAE reporting, sign-off for medical exam queries, exam result interpretation [e.g. lab reports]) that were later removed when the EDSS assessment task was assigned (1/2016). The extent to which these delegated tasks were performed by EDSS investigators is not known. Per protocol, the examining EDSS investigator

would have access only to the EDSS/FSS data.

There was no evidence of underreporting of adverse events, and no SAEs were reported at this site.

*Reviewer comments: For Subject (b) (6) queries were sent to the site after the relapse had occurred and included queries of the baseline EDSS scores, which had been completed 6 weeks prior. It is unknown when the CEC reviewed the data, including EDSS scores, to determine whether the relapse met criteria for a protocol-defined relapse.*

*While there was no evidence that the blind was compromised for the examining investigators who conducted the EDSS assessments, the task assignments in the delegation log indicated that this site may not have been diligent in shielding the examining investigators from study-related information that could have compromised the blind.*

*{See appended electronic signature page}*

Cara Alfaro, Pharm.D.  
Clinical Analyst  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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Kassa Ayalew, M.D., M.P.H  
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Good Clinical Practice Assessment Branch  
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Office of Scientific Investigations

**cc:**

Central Document Room/BLA #761149  
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Division of Neurology 2/Medical Team Leader/Paul Lee  
Division of Neurology 2/Medical Officer/Lawrence Rodichok  
Division of Neurology 2/Project Manager/Susan Daugherty  
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OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein  
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro  
OSI/GCPAB Program Analyst/Yolanda Patague



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CARA L ALFARO  
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04/06/2020 02:56:00 PM

KASSA AYALEW  
04/06/2020 03:05:16 PM



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** October 22, 2019

**To:** Billy Dunn, M.D., Director  
Division of Neurology Products

**Through:** Dominic Chiapperino, Ph.D., Director  
Controlled Substance Staff

**From:** Silvia N. Calderon Ph.D., Senior Pharmacologist  
Controlled Substance Staff

**Subject:** BLA761149 Satralizumab (anti-IL-6 receptor antibody) injectable for subcutaneous administration

**Indication:** [REDACTED] (b) (4)  
[REDACTED] for the treatment of adult [REDACTED] (b) (4)  
[REDACTED] with neuromyelitis optica spectrum disorder (NMOSD)

**Dosages:** 120 mg/mL in a single-dose prefilled syringe

**Sponsor:** Genentech

**Materials reviewed:** BLA761149 for filing purposes.  
IND 118183, CSS review DARRTS, Hunt, Joshua S, 3/21/2017

## **I. Background**

This memorandum is in response to a consult request dated August 19, 2019, from the Division of Neurology Products pertaining the fileability of BLA 761149, Enspryng (Satralizumab) injectable solution for subcutaneous administration, and in lieu of a filing checklist.

Satralizumab was developed by Chugai Pharma USA, INC, under IND 118183, and it was known by the names of SA237 and sapeluzimab. While the biologic was under development, CSS was asked by the Division to address the abuse potential of Satralizumab. CSS communicated to the Sponsor at a Type C meeting that took place on March 28, 2017, that the drug did not demonstrate CNS activity and consequently CSS was not recommending conducting animal or human abuse potential studies. CSS requested the Sponsor to monitor clinical trials for the occurrence of abuse-related adverse events (AEs). In the current BLA submission, the Sponsor states that a review of clinical AEs demonstrated that the drug lacks psychoactive effects.

## **II. Conclusions**

1. CSS previously reviewed satralizumab under IND 118183 and concluded it did not demonstrate CNS activity. However, the Sponsor was asked to monitor for the occurrence of abuse-related AEs in clinical trials.
2. The current Sponsor claims that no abuse-related AEs were reported in clinical trials.

### **III. Recommendations to the Division**

Based on CSS's prior findings for satralizumab stated above and the Sponsor's assertion that no CNS abuse-related adverse events were reported in clinical trials, we believe that CSS need not be involved in the review of this BLA. Consequently, ***CSS will not submit a filing checklist for BLA 761149.***

CSS requests that the Division consult CSS if the DNP review team identifies any abuse-related concerns associated with the drug through the course of their review of this BLA.

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SILVIA N CALDERON  
10/22/2019 12:47:06 PM

DOMINIC CHIAPPERINO  
10/23/2019 01:47:13 PM



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** September 12, 2019

**To:** Billy Dunn, M.D., Director  
Division of Neurology Products

**Through:** Dominic Chiapperino, Ph.D., Director  
Controlled Substance Staff

**From:** Silvia N. Calderon Ph.D., Senior Pharmacologist  
Controlled Substance Staff

**Subject:** BLA761149 Satralizumab (anti-IL-6 receptor antibody) injectable for subcutaneous administration

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**Materials reviewed:** BLA761149 for filing purposes.  
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