CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761369Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 126734
Request Receipt Date	10/5/2023
Product	marstacimab
Indication	Routine prophylaxis in hemophilia A and hemophilia B patients and hemophilia A and hemophilia B patients with inhibitors to factor VIII or factor IX.
Drug Class/Mechanism of Action	monoclonal antibody targeting tissue factor pathway inhibitor (TFPI)
Sponsor	Pfizer Inc.
ODE/Division	Division of Nonmalignant Hematology
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	12/4/2023

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   The proposed indication for marstacimab is for the routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with:
   - hemophilia A (congenital FVIII deficiency) without FVIII inhibitors, or
   - hemophilia B (congenital FIX deficiency) without FIX inhibitors.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Marstacimab is a monoclonal antibody targeting tissue factor pathway inhibitor (TFPI) and thereby impacts the extrinsic pathway of the coagulation system. In both hemophilia A and B, there is an inability to generate sufficient amounts of thrombin that ultimately leads to a downstream lack of insoluble fibrin generation, which is needed for clot formation. Inhibition of TFPI activity with marstacimab represents an approach to increase the production of thrombin, and thus clotting in patients with hemophilia A and B. The Sponsor is developing marstacimab for patients with hemophilia A and B without inhibitors. Of note, the Sponsor is also developing marstacimab for hemophilia A and B with inhibitors, but this data is not yet available and therefore the indication in patients with hemophilia A and B with inhibitors is not included in this BTDR.

Hemophilia A and B without inhibitors are rare, serious, life- threatening diseases characterized by bleeding due to an inherited X-linked recessive Factor VIII deficiency (hemophilia A or HA) or Factor IX deficiency (hemophilia B or HB). Bleeding into the muscle, soft tissue, and joints (hemarthroses) can occur spontaneously or by trauma. Examples of bleeding events include intracranial hemorrhage, deep muscle and joint hemorrhage, hematomas, retroperitoneal hemorrhage, bleeding following tooth extraction, post-surgical bleeding, easy bruising, and mucosal bleeding.

Available therapies for the proposed indications include numerous factor products (plasma factor and recombinant factor) with standard half-life or extended half-life. Treatment with the replacement coagulation factor can either be episodic, treating bleeding episodes on-demand (OD) as they occur, or prophylactic, preventing bleeding episodes by a regular schedule of FVIII or FIX infusions to maintain factor levels in a range >1%. Significant evidence exists that prophylactic treatment prevents serious and non-serious bleeding episodes(1). Regular intravenous (IV) infusions with factor are required at frequencies ranging from twice weekly, to once every 2 weeks for prophylaxis. With factor infusions, there is a risk of FVIII (hemophilia A) or FIX (hemophilia B) inhibitor development. Inhibitors can decrease the efficacy of factor replacement and increase risk of morbidity and mortality. There is also a risk of thromboembolism.

Non-factor therapies approved for hemophilia include Emicizumab (Hemlibra), a bi-specific antibody that bridges activated coagulation Factor IXa and Factor X and is an approved non-factor based prophylactic therapy for patients with hemophilia A. Emicizumab is approved for once weekly (QW) administration for the first 4 weeks, followed by subcutaneous (SC) administration weekly, or every 2 or 4 weeks. There is a boxed warning for thromboembolism and thrombotic microangiopathy. In addition, there is a risk of development of neutralizing antibodies which can lead to loss of efficacy. Most recently, a gene therapy products are available, hemgenix (etranacogene dezxaparvovec-drlb) is a gene therapy treatment approved in the US for treatment of adults with hemophilia B and Roctavian (valoctocogene roxparvovec) is a gene therapy treatment that has been approved for the treatment of hemophilia A. However, these therapies is not accessible to the majority of patients and have serious risks including thromboembolism and malignancy.

If approved, marstacimab would offer a non-factor based prophylactic therapy option to patients with hemophilia A and B without inhibitors and can be administered by SC injection.

The Sponsor had a preliminary BTDR Advice Meeting on September 20, 2023 at which the Division told the Sponsor they would need to demonstrate a substantial improvement in a clinically significant endpoint for each subgroup of patients for which BTD is being sought. The Sponsor submitted the BLA for the proposed indications on October 11, 2023.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary efficacy endpoint was the annualized bleeding rate (ABR) of treated bleeds.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The primary endpoint of annualized bleeding rate (ABR) from the pivotal study, Study B7841005, is a direct measure of clinical benefit and has been used in other clinical development programs to support approval for other FDA approved hemophilia therapies.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Table 1. describes available therapies for patients with hemophilia A or B without inhibitors for primary prophylaxis. When available, the efficacy endpoint of interest was ABR for all products. Standard of care consists of factor therapy and emicizumab (Hemlibra).

Table 1. Available Therapies

Drug	Population	Endpoint	Treatment effect
Plasma factor			
Alphanate	HA	Not described	Not described
AlphaNine SD	HB	Not described	Not described
Recombinant Factor			

Afstyla	HA	ABR	The ABR in prophylaxis (median of 1.14) was significantly lower (p <0.0001) than the ABR that was observed in subjects treated on-demand (median of 19.64).
Altuviiio	HA	ABR	Routine prophylaxis resulted in a mean ABR (95% CI) of 0.7 (0.5, 1.0), a median (Q1, Q3) ABR of 0 (0, 1.0), and a median (Q1, Q3) annualized joint bleeding rate of 0 (0, 1.0).
Eloctate	HA	ABR	Using a negative binomial model to analyze the annualized bleeding rate (ABR), there was a statistically significant reduction in ABR of 92% (p<0.001) for subjects in the individualized prophylaxis arm and a statistically significant reduction of 76% (p<0.001) for subjects in the weekly prophylaxis arm compared to the episodic (on-demand) arm.
Esperoct	HA	ABR	The median annualized bleeding rate (ABR) for treated bleeds in adults and adolescents treated every 4 days was 1.2 (IQR: 0.0:4.3), and mean ABR was 3.0 (SD: 4.7)
Jivi	HA	ABR	An analysis compared ABRs between the on-demand group and the different prophylaxis regimens indicated that the ABR was significantly reduced by 88.2% in the every 5-days (p<0.0001) in comparison with on-demand treatment.
Kogenate	HA	ABR	Patients who received prophylaxis experienced statistically significantly fewer bleeds (p<0.0001) compared to patients treated ondemand regardless of baseline subgroups examined including age, bleeding history, and presence or absence of target joints. The ratio of the mean bleeding frequency was 15.2 (95% CI: 8.5, 27.2; p<0.0001) for on-demand versus prophylaxis.
Kovaltry	HA	ABR	The mean and median ABR for the ITT population in Trial 1 was 3.8 ± 5.2 and 1 bleed/year, respectively. In Trial 2, comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis in an ANOVA demonstrated a statistically significant difference (p<0.0001) in the median ABR in subjects receiving on-demand therapy (60 bleeds per year) as compared to subjects receiving prophylaxis (2 bleeds per year). In Trial 2, mean ABR in subjects receiving on-demand therapy was 57.7 ± 24.6 versus 4.9 ± 6.8 in the subjects receiving prophylaxis.
Nuwiq	HA	ABR	Adults: 1.16 ± 2.57 (median 0, range 0-8.6) Pediatrics: 1.50 ± 3.32 (median 0, range 0-13.8)
Alprolix	HB	ABR	Using a negative binomial model, a reduction in annualized bleeding rate (ABR) of 83% (76-89%) for subjects in the fixed weekly interval arm and a reduction of 87% (80%-92%) for subjects in the individualized interval arm compared to the episodic (on-demand) treatment arm was observed.
BeneFIX	HB	ABR	the annualized bleedrate (ABR) for the prophylaxis period was significantly lower (p < 0.0001) than the ABR for the on-demand period (mean ± standard deviation (SD): 3.6 ± 4.6, median: 2.0, min-max: 0-13.8 versus mean: 32.9 ± 17.4, median: 33.6, min-max: 6.1-69.0, respectively).
Idelvion	HB	ABR	The median annualized bleeding rate (total ABR – spontaneous and traumatic) during prophylaxis treatment was 1.6; (range: 0 to 21.1), as compared to 19.2; (range: 2 to 46.1) during on-demand treatment. Based on the Poisson model, prophylaxis treatment with IDELVION resulted in an 88% reduction in the annualized bleeding rate.
Rixubis	HB	ABR	In the on-demand arm, the mean treatment duration was 3.5 ± 1 months (median 3.4, ranging from 1.2 to 5.1 months) and the mean total annualized

			bleeding rate (ABR was 33.9 ± 17.37 with a median of 27 ranging from 12.9 to 73.1. In the prophylaxis arm the mean ABR was 4.3 for all bleeds, 1.7 for spontaneous bleeds, and 2.9 for joint bleeds
Antibody Therapy			
Hemlibra	HA	ABR	ABR at 1.5mg/kg was 1.5 (95% CI: 0.9, 2.5), 3mg/kg was 1.3 (95% CI: 0.8, 2.3) and no prophylaxis was 38.2 (95% CI: 22.9, 63.8). intra-patient analysis, HEMLIBRA prophylaxis resulted in a statistically significant ($p < 0.0001$) reduction (68%) in bleed rate for treated bleeds compared with previous FVIII prophylaxis
Gene Therapy			
Roctavian	HA	ABR	The mean efficacy evaluation period ABR was 2.6 bleeds/year, compared to a mean baseline ABR of 5.4 bleeds/year. The mean difference in ABR was -2.8 (95% confidence interval: -4.3, -1.2) bleeds/year.
Hemgenix	HB	ABR	The estimated mean ABR during Months 7 to 18 after HEMGENIX treatment was 1.9 bleeds/year with a 95% confidence interval (CI) of (1.0, 3.4), compared with an estimated mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio (Months 7 to 18 post-treatment / lead-in) was 0.46 [95% CI: 0.26, 0.81], demonstrating non-inferiority of ABR during Months 7 to 18 compared to the lead-in period.

Abbreviations: ABR=annualized bleeding rate, HA= hemophilia A, HB= hemophilia B

*Data was obtained from FDA USPIs

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Concizumab (b) (4) received BTD but this was for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia B patients with inhibitors. Patients with inhibitors have increased risk of morbidity and mortality and have very few treatment options. Similarly, emicizumab was granted breakthrough therapy designation for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years old withhemophilia A with FVIII inhibitors.

11. Information related to the preliminary clinical evidence:

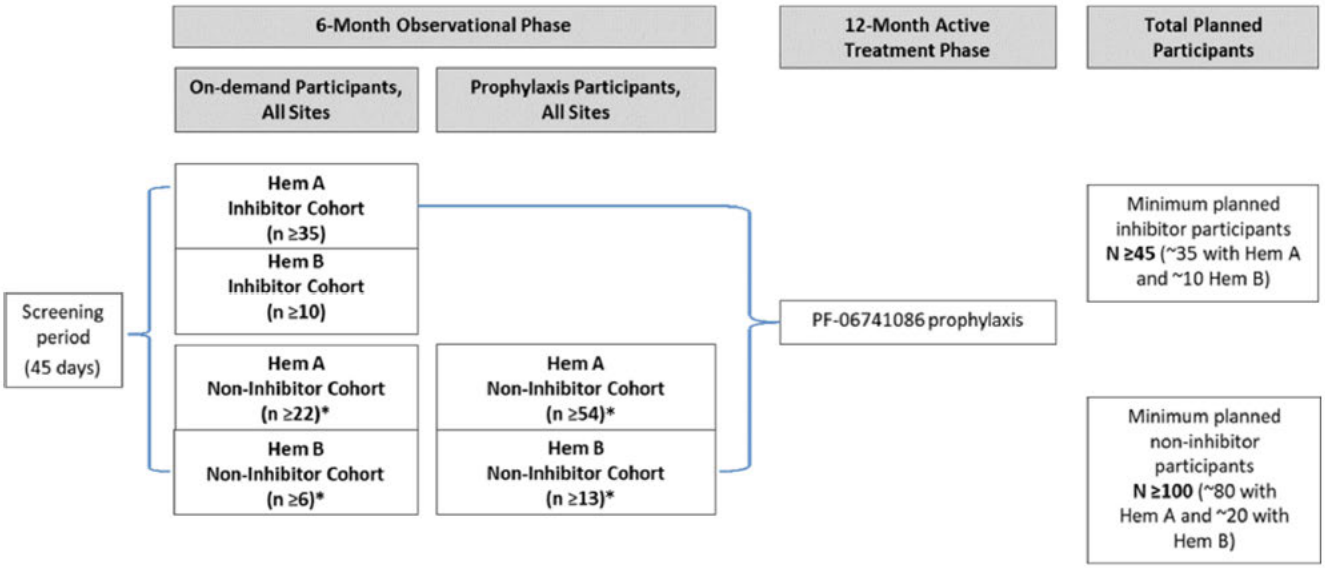
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study B7841005 is a phase 3, one-way switch, open-label, multi-center study in adolescent and adult participants between ages 12 to <75 years with severe hemophilia A or moderately severe to severe hemophilia B (defined as FVIII activity <1%, or FIX activity ≤2%, respectively) with or without inhibitors. This study compares treatment with prescribed factor replacement therapy or bypass therapy during an Observational Phase (OP) with a 12-month Active Treatment Phase (ATP), during which participants will receive prophylaxis (defined as treatment by SC

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

injection of marstacimab). The study schema is shown in the figure below, only the non-inhibitor cohort data was shared with the Agency for this BTDR. Patients receiving routine prophylaxis (defined as treatment by IV injection of factor concentrate to prevent bleeding) treatment with FVIII/FIX replacement must have demonstrated at least 80% compliance with scheduled prophylaxis regimen during 6 months prior to enrollment and patients on on-demand treatment regimen must have ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion during the 6 months period prior to enrollment into the Observational Phase.

Figure 1. Study B7841005 Schema



Source: Sponsor's Protocol

The primary endpoint was the ABR of treated bleeding events. This was measured by the ratio of the mean ABR (marstacimab prophylaxis vs on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy. In total, the on-demand cohort (patients received on-demand factor therapy in the 6-month observational phase) included 33 patients, of which 26 patients had hemophilia A and 7 patients had hemophilia B. The study met the primary endpoint of demonstrating marstacimab prophylaxis superiority over on-demand therapy. The on-demand mean estimated ABR was 38 (95% CI: 31.03, 46.54) in the OP, compared to the mean marstacimab ABR was 3.18 (95% CI: 2.09, 4.85) in the ATP. The estimated ABR ratio was 0.084 (95% CI: 0.059, 0.119, 2-sided p-value <0.0001), which corresponded to a reduction in ABR of treated bleeds to 91.6%. In a post-hoc analysis submitted to the BLA, the results were consistent in hemophilia A and hemophilia B subgroups.

The mean ABR difference between marstacimab prophylaxis and the routine prophylaxis was a secondary endpoint. In total, the prior prophylaxis cohort included 83 patients, of which 65 had hemophilia A and 18 had hemophilia B. The study met the secondary endpoint of marstacimab prophylaxis (ATP) demonstrating non-inferiority to routine prophylaxis (OP). The routine prophylaxis mean estimated ABR was 7.85 (95% CI: 5.09, 10.61) in the OP compared to the marstacimab ATP mean estimated ABR was 5.08 (95% CI: 3.40, 6.77). This corresponded to the estimated ABR difference of -2.77 (95% CI: -5.37, -0.16), which was lower than the upper bound of the 95% CI for the ABR difference less than 2.5, which was the predetermined criteria for establishing non-inferiority. Superiority could not be claimed due to the hierarchical nature of the testing sequence. Results were similar in the post-hoc subgroup analysis by hemophilia type, although the ABR was slightly higher in the hemophilia B marstacimab group, compared to the observational phase. Results of the subgroups are difficult to interpret given the small sample size.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

In the phase 3 study B7841005, marstacimab was well tolerated with low rates of serious adverse events (SAEs) and AEs leading to discontinuation. Frequent adverse reactions were due to injection site reactions. Of note, during the 12-month treatment period in Study B7841005, 23 out of 116 evaluable participants (19.8% incidence) tested positive for anti-drug antibodies (ADA) for marstacimab and out of the 23 patients 26.1% tested positive for Neutralizing Antibodies. ADAs resolved in all participants except 1 patient by the end of study. Per the Sponsor, there was no clinically meaningful impact, however this data has not yet been reviewed by the Division.

Also, one subject in a healthy volunteer study developed a pulmonary embolism, this case is confounded by concomitant administration of a COVID-19 vaccine.

12. Division's recommendation and rationale (pre-MPC review):

☐ GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☒DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

Hemophilia A and B without inhibitors are rare, serious diseases with an unmet need for new therapies. While the Sponsor has achieved the primary endpoint of superiority of marstacimab prophylaxis over on-demand factor therapy on a clinically meaningful endpoint, ABR, the Sponsor has not demonstrated substantial improvement over existing therapies. The Sponsor has clearly demonstrated the treatment effect of marstacimab by assessing the magnitude of improvement in ABR compared to on-demand factor therapy. However, to demonstrate substantial improvement over available therapies a comparison to factor prophylaxis (for hemophilia A and hemophilia B) and/or emicizumab prophylaxis (for hemophilia A) is needed. While non-inferiority was met on this endpoint, superiority was not, thus it does not appear marstacimab is better than available therapies.

In addition, there seems to be a significant development of ADAs, whether this may impact the efficacy of marstacimab is not clear at this time. Lastly, there is no significant safety advantage compared to available therapies.

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

As the Sponsor's study is complete and submitted as a new BLA application, BTD appears unlikely for the proposed indication at this time. However, if the Sponsor has promising data of marstacimab prophylaxis for patients with hemophilia A or B with inhibitors, this could be one approach to reconsider BTD.

14. List references, if any:

1. Srivastava, Alok, et al. "WFH guidelines for the management of hemophilia." Haemophilia 26 (2020): 1-158.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☒

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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.

/s/

CARRIE E DIAMOND
12/06/2023 08:47:40 AM

TANYA M WROBLEWSKI
12/07/2023 08:36:56 AM

IND 126734

MEETING MINUTES

Pfizer Inc
Attention: Mary Kate Whitecavage
Director, Pfizer Global Regulatory Sciences
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Whitecavage:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06741086.

We also refer to the teleconference between representatives of your firm and the FDA on June 21, 2023. The purpose of the meeting was to discuss the proposed submission of a BLA for PF-06741086.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Carrie Diamond, MD
Clinical Team Leader
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	June 21, 2023, 3:00p.m.- 4:00p.m. (EDT)
Meeting Location:	Teleconference
Application Number:	IND 126734
Product Name:	PF-06741086
Indication:	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A or B patients without inhibitors ages 12 years and older
Sponsor Name:	Pfizer Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Carrie Diamond, MD
Meeting Recorder:	Courtney Hamilton, PharmD

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), Division of Nonmalignant Hematology (DNH)
Tanya Wroblewski, MD, Deputy Director (Acting)
Rosanna Setse, MD, MPH, PhD, Deputy Director for Safety
Carrie Diamond, MD, Clinical Team Lead
Andrew Dmytrijuk, MD, Clinical Reviewer

Division of Pharmacology & Toxicology (DPT-OCHEN)
Todd Bourcier, PhD, Director
Fred Alavi, PhD, Nonclinical Reviewer

Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Lead
Anusha Ande, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Supervisor
Lola Luo, PhD, Statistical Reviewer

Office of Regulatory Operations (ORO), Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)
Courtney Hamilton, PharmD, BCPS, Senior Regulatory Project Manager
Sejal Kiani, MS, Chief, Project Management Staff (Acting)

SPONSOR ATTENDEES
Kate Betteridge, PhD, Senior Director, Global Regulatory Portfolio Lead
Francesca Biondo, MD, Senior Director, Medicine Team Lead Hemophilia
Greg DiRusso, MD, FACS Development Head Benign Hematology
Iwona Jeske Dupont, PhD, Vice President, Global Regulatory Sciences Rare Disease
Jill Hubbard, MS, Senior Manager, Global Regulatory Sciences CMC Devices
Eunhee Hwang, PhD, Director, Biostatistics
Tim Kluge, Director, Statistical Programming and Analysis
Iyar Mazar, PhD, Director, Patient-Centered Outcomes Assessment
Regina McDonald, Senior Director, Clinical Study Team Lead
Cindy Osborn, PhD, Senior Manager, Global Regulatory Sciences CMC
Debra Pittman, MS, Senior Research Director, Nonclinical Pharmacology
Sangeeta Raje, PhD, Director, Clinical Pharmacology
Christine Seymour, PhD, Senior Director, Global Regulatory Sciences CMC
Ann Subashi, PhD, Senior Director, Global Regulatory Sciences CMC
John Teeter, MD, Senior Director, Global Product Development
Carrie Turich Taylor, PhD, MHS, Senior Director, Safety Surveillance and Risk Management
Mary Kate Whitecavage, MS, Director, Global Regulatory Sciences
Jessica E. Whritenour, PhD, Associate Research Fellow, Drug Safety Research and Development

1.0 BACKGROUND

PF-06741086, also referred to as marstacimab, is a fully human antibody IgG1 immunoglobulin. It targets the functional K2 domain of tissue factor pathway inhibitor (TFPI), which interacts with FXa, and binds with low nanomolar affinity.

Notable programs for marstacimab include orphan drug designation (16-5219) on May 18, 2016, for treatment of Hemophilia A (HA) and Hemophilia B (HB) patients with or without inhibitors which includes routine prophylaxis to prevent or reduce the frequency of bleeding in HA and HB patients, as well as, Fast Track Designation granted on September 17, 2019, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in HA with inhibitors or HB with inhibitors.

The purpose of the requested Type B meeting is to discuss the initial phase 3 study results in Hemophilia A and B participants without inhibitors and the proposed submission of a BLA for PF-06741086. More specifically the meeting objectives include:

- appropriateness of the draft table of contents of the BLA

- the sufficiency of the safety and efficacy data supporting a positive benefit risk profile for the use of marstacimab in patients with hemophilia, without inhibitors
- structure and content of safety narratives, SDSP, and the 4-month safety update following initial BLA submission
- supportive information for patient reported outcomes
- proposed commercial presentation of a prefilled pen (PFP)
- proposal for Priority Review of the BLA
- submission requirements with respect to orphan designation

Pfizer proposes to submit a BLA to support marstacimab in August 2023. The intended initial indication will be for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with:

- hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or
- hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

FDA sent Preliminary Comments to Pfizer Inc. on June 15, 2023.

2.1. Questions and Responses

Question 1: Does the FDA agree that the proposed CMC data package as described in the Table of Contents (TOC) for Module 3, is sufficient to support a BLA filing and review?

FDA response to Question 1: The provided Table of Contents appears reasonable. The adequacy of the data and information provided in each section will be a review issue.

Meeting Discussion: No meeting discussion took place.

Question 2: Does the Agency agree that the completed nonclinical studies as summarized in the TOC for Module 4 (Appendix 5) constitutes a thorough nonclinical program that is adequate to support review of the BLA for marstacimab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with:

- hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or
- hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

FDA response to Question 2: Yes, we agree. The completed nonclinical studies are sufficient to support review of the marstacimab BLA. As noted in previous communications, we ask you to provide a risk assessment based on weight of

evidence analysis as described in S1B(R1) Addendum of guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals*[1].

Meeting Discussion: No meeting discussion took place.

Question 3: Pfizer proposes to submit an initial BLA with safety and efficacy data from the Phase 3 Study B7841005 and OLE Study B7841007, with at least 12 months of efficacy data available from 116 participants to support the initial registration package for marstacimab.

Does the Agency agree that the Phase 3 and safety results support filing and review of the BLA for marstacimab for the proposed indication and presentations?

FDA response to Question 3: You have proposed to submit a BLA based on the results of the phase 3 study B7841005[2] and the open-label extension (OLE) study B7841007[3] to support an indication of routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with HA and HB without inhibitors. Study B7841005 is a single-arm, one-way switch study, designed to compare efficacy and safety of participants' prescribed factor replacement therapy during a 6- month observation phase (OP) versus marstacimab prophylaxis over a 12-month active treatment phase (ATP) in participants with severe HA or HB with or without inhibitors. The non-inhibitor cohort consisted of two groups based on the type of prescribed factor replacement treatment during the OP: on-demand (OD) or routine prophylaxis (RP). A total of 116 patients (33 and 83 from the OD and RP groups, respectively) completed the OP and received at least one dose of marstacimab in the ATP and were evaluated for marstacimab safety and efficacy.

You state marstacimab achieved the primary endpoint of demonstrating superiority over OD as measured by annualized bleeding rate (ABR) of treated bleeds. The mean ABR was 3.18 (95% CI: 2.09, 4.85) on marstacimab compared to the mean ABR of 38.00 (95% CI: 31.03, 46.54) on OD during the OP, with an ABR ratio of 0.084 (95% CI: 0.059, 0.119, p-value <0.0001). The key secondary endpoint was also achieved, marstacimab demonstrated non-inferiority over RP treatment as measured by ABR of treated bleeds. The mean ABR was 5.08 (95% CI: 3.40,

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[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%) Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis
[3] An Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Marstacimab Prophylaxis in Severe (Coagulation Factor Activity <1%) Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia A and B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors

6.77) on marstacimab compared to the mean ABR of 7.85 (95% CI: 5.09, 10.61) on RP during the OP with an ABR difference of -2.77 (95% CI: -5.37, -0.16). Marstacimab also demonstrated superiority (2-sided p-value = 0.0376) over RP treatment. You state superiority of marstacimab vs. OD was demonstrated for all key secondary endpoints except for the HRQoL endpoint. The most common adverse event was injection site reactions, most of which you state were mild or moderate. No thromboembolic events have occurred across the development program.

It is not clear at this time if your clinical package is sufficient to support the submission of the BLA. While the topline results presented above from your phase 3 study appear acceptable to support a BLA submission, you have not described how you plan to demonstrate substantial evidence of effectiveness. In the Type C Meeting Preliminary Comments dated July 14, 2022, we asked you to clarify your plans for establishing substantial evidence of effectiveness. As it appears you are planning on submitting one adequate and well controlled trial, you will need to provide strong confirmatory evidence as described in the guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*. Please note, whether a clinical package is sufficient for filing and review will be determined after a BLA is submitted. In addition, please see several comments below.

Additional Comments:

a) **Please clarify the current status of the inhibitor cohort from Study B7841005 and the pediatric Study B7841008[4] (i.e., how many patients enrolled, exposure data and estimated completion dates of the trials).**

b) **As this is a single-arm, open-label study in which all patients were aware they were receiving marstacimab, we are concerned that patients may have altered their behavior knowing they were on marstacimab and this could favor the study drug. Please clarify how you intend to address this concern in your submission.**

c) **The proposed dosing regimen is marstacimab 300 mg loading dose followed by 150 mg subcutaneous (SC) once weekly (QW). Individual participants who meet protocol specified dose escalation criteria based on breakthrough bleeding, had the option to dose escalate to 300 mg SC QW. Please clarify how many patients required dose escalation.**

[4] An Open-Label Study in Pediatric (<18 Years of Age), Severe Hemophilia A Participants (Coagulation Factor Activity <1%) With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing 12 Months of Historical Standard Treatment to Marstacimab Prophylaxis

Meeting Discussion: **The Sponsor provided additional details on their plans for submitting one adequate and well-controlled study with confirmatory evidence to establish substantial evidence of effectiveness.**

The Agency reiterated the recommendation to submit two adequate and well-controlled studies, however, the Sponsor's proposal may be reasonable. If the Sponsor chooses to submit one adequate and well controlled trial with confirmatory evidence, the Agency recommended that the Sponsor include a detailed description of the confirmatory evidence they plan to submit to support substantial evidence of effectiveness with their BLA submission.

(b) (4)

The Sponsor provided additional rationale and steps taken to minimize bias associated with the open-label design of the study. The Agency recommended to submit this rationale with the BLA submission and this will ultimately be a review issue.

The Sponsor stated that in study BF841005, 14 patients (12.1%) were escalated to a dose of 300mg SC weekly in the non-inhibitor cohort. The Sponsor stated that the higher dose was effective and there was no difference in the toxicity profile of the higher dose of marstacimab compared to the lower dose. The Sponsor will provide details regarding dose escalations in the BLA submission.

The Agency also stated they would provide post meeting comments regarding claims of superiority.

Post Meeting Comments:
You stated that marstacimab demonstrated superiority (2-sided p-value = 0.0376) over RP for treated bleeds. We do not agree. According to the most recent SAP(v6), dated January 31, 2023, the superiority test of marstacimab vs prior prophylaxis is listed as #12 in the testing sequence, however, according to the submitted top line results (IND 126734, Seq#0166) dated, May 31, 2023, the superiority test of marstacimab vs. on-demand for the key secondary endpoint, physical function domain in Haem-A-QoL, listed as #11 in the testing sequence, did not yield a statistically significant result (p-value=0.1161). Hence, the results for all subsequent testing in the testing sequence should only be considered exploratory in order to control the FWER within 2-sided alpha level of 0.05. The Agency would like to reiterate that exploratory results should not be used to make any inferential conclusions or for labeling claims.

Question 4: The Agency previously agreed on the criteria of the patient safety narratives (Type C meeting, July 2022, Appendix 2). Two example safety narratives from completed CSRs (Study B7841003 and Study B7841009) are provided to demonstrate the format and information to be provided in the safety narratives supporting the BLA submission.

Does the Agency agree with the proposed structure and format of the safety narratives?

FDA response to Question 4: We agree with the proposed structure and format of the safety narratives. You should include narratives for any patients with serious adverse events, adverse events of special interest (e.g., cutaneous skin reactions; cases meeting Hy's law criteria; etc.). Also, include narrative details for patients who were prematurely discontinued from the study for any reason.

Meeting Discussion: No meeting discussion took place.

Question 5: Pfizer intends to submit CDISC compliant datasets as described in the Company Position. Does the FDA agree that the outlined SDSP as provided is sufficient to support the review of the BLA?

FDA response to Question 5: From the technical perspective (format standpoint) the outlined Study Data Standardization Plan (SDSP) for supporting the review of the BLA is acceptable.

For the program file submission, please follow Study Data Technical Conformance Guide 4.1.2.10 Software Programs and be aware of "Files with MS Windows executable extensions (.cmd, .com, and .exe) should NOT be submitted".

Additional Statistical Comments:

a) **We request that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), be prepared and submitted in the BLA. Please refer to the technical specifications document *Study Data Technical Conformance Guide*.**

b) **Provide comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.**

c) **For the major efficacy and safety studies, in addition to the study data, we also have the following requests:**

   i. **Provide executable SAS programs with adequate document(s) to allow FDA to derive the analysis datasets from the raw datasets you submitted.**

ii. **Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.**

iii. **Include all study protocols, amendments, and meeting minutes as well as related materials discussed during IND meetings.**

Meeting Discussion: The Agency stated that the Sponsor's proposal appears reasonable.

Question 6a: Does the Agency agree with the proposed cutoff dates indicated below (Table 2) for the safety updates for the ongoing inhibitor cohort from Study B7841005 and both ongoing non-inhibitor and inhibitor cohorts from extension Study B7841007 and pediatric Study B7841008?

FDA response to Question 6a: The cutoff dates for the safety update will depend on whether the application qualifies for priority review. A 4-month update is required for priority review while a 6-month update will be required for standard review. You should include the type of review requested at the time you file your application.

Meeting Discussion: The Agency clarified that it is expected that the Sponsor will submit a 4-month safety update. If priority review is granted, the Sponsor should submit a 3-month safety update.

Question 6b: Pfizer proposes the content of the 4-month safety update will only include key safety data as defined in the company position from all ongoing clinical studies; does the Agency agree?

FDA response to Question 6b: Inclusion of safety data from the ongoing studies, including the ongoing inhibitor cohort from Study B7841005 and both ongoing non-inhibitor and inhibitor cohorts from extension Study B7841007 and pediatric Study B7841008, is acceptable.

Meeting Discussion: No meeting discussion took place.

Question 7: Pfizer will submit a Clinical Outcome Assessment (COA) Evidence Dossier supporting the electronic Hemophilia Bleed and Infusion Diary (eHBAID) as a validated instrument that captures patient-reported outcomes, including bleed, infusion, and treatment logs. Based on the draft table of contents included in Appendix 7, does the Agency agree that the dossier will provide the appropriate supportive evidence for the primary and secondary endpoints to include in the USPI based on the eHBAID, and that the dossier should be included in Module 5.3.5.3?

FDA response to Question 7: At this time, we cannot comment on the appropriateness of the evidence without reviewing it. However, the content that you plan to submit within the evidence dossiers appears reasonable. We refer you to the Appendix of the FDA guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and Appendix E of guidance for industry *Food and Drug Administration Staff, and Other Stakeholders: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* regarding what evidence to submit for review.

Meeting Discussion: No meeting discussion took place.

Question 8: Pfizer will submit a COA Evidence Dossier supporting the Haem-A-QoL/Haemo-QoL as a fit-for-purpose measure of physical health in the target patient population. Based on the draft table of contents included in Appendix 8, does the Agency agree that the dossier will provide the appropriate supportive evidence for the Haem-A-QoL/Haemo-QoL-based secondary endpoint to include in the USPI, and that the dossier should be included in Module 5.3.5.3?

FDA response to Question 8: See FDA response to Question 7.

Meeting Discussion: No meeting discussion took place.

Question 9: Does the Agency agree that the proposed summary and presentation of the immunogenicity assessments are sufficient to support review of the planned BLA?

FDA response to Question 9: Your plan to include the assessment of marstacimab immunogenicity in an Integrated Summary of Immunogenicity (ISI) is acceptable. You plan to incorporate the elements of a comprehensive review of immunogenicity including clinical antibody assay methods and performance, clinical trial immunogenicity testing hierarchy and assay cut points, results of immunogenicity analyses, including the incidence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) and titers along with results of analyses of the effect of ADAs and NAbs on marstacimab efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD).

Meeting Discussion: The Sponsor elaborated on the proposed plan for submitting immunogenicity data. Immunogenicity data for 112 out of 116 non-inhibitor hemophilia participants will be included in the original BLA submission. Due to assay transfer issues to the local lab, analysis of ADA and NAb data for 4 Chinese non-inhibitor participants is delayed. The Sponsor stated that efficacy, safety, PK and PD data are available for these 4 participants and show no clinically relevant differences in comparison to the overall patient profile; therefore, the evidence suggests that the presence of marstacimab ADAs or NAbs is not associated with safety concerns as reflected by the incidences of SAEs; AEs; AESIs such as

immunogenicity, hypersensitivity, or injection site reactions; or other clinical sequelae as presented in the BLA submission. In addition, annualized bleeding rates for these 4 participants are 1.02, 2.04, 0.00 and 2.04.

In the event the ADA/NAb data for the 4 Chinese non-inhibitor participants is not available at the time of BLA submission, the Sponsor requested to submit the ADA/NAb data and relevant analyses for these 4 participants within 30 days of the BLA submission.

The Agency agreed with the Sponsor's proposal to submit the immunogenicity data within 30 days of the BLA submission.

Question 10: Does the Agency agree that these data, in addition to the device data that will be provided in Module 3 of the BLA, will provide a sufficient data package for registration of the marstacimab PFP presentation?

FDA response to Question 10: You plan to provide the final Clinical Study Report (CSR) for the Study B7841009[5], which established bioequivalence between the marstacimab prefilled syringe (PFS) and PFP administration presentations, and interim CSR for the phase 3 extension Study B7841007 in which participants enrolled from pivotal phase 3 Study B7841005 have transitioned from use of the PFS to PFP for the administration of marstacimab. You also plan to provide the final CSR for the marstacimab open-label, single arm PFP substudy of Study B7841007. We agree that your proposal seems reasonable.

Meeting Discussion: No meeting discussion took place.

Question 11: Pfizer has provided a Table of Contents for the planned BLA package in Appendix 5, does the Agency agree:

a. that the proposed presentation of biopharmaceutical and analytical method information within the SBS (Module 2.7.1) as outlined in the TOC is appropriate to support the review of the planned BLA?

b. that the proposed presentation of clinical pharmacology information within the SCP (Module 2.7.2) as outlined in the TOC is appropriate to support the review of the planned BLA?

c. the proposed presentation of efficacy information within the SCE (Module 2.7.3) as outlined in the TOC is appropriate to support the review of the planned BLA?

[5] A Phase 1, Open-Label, Randomized, 4-Period, 2 Sequence, Crossover Study To Evaluate The Bioequivalence Of Marstacimab (PF-06741086) Prefilled Syringe Device And Prefilled Pen Device Following Subcutaneous Administration In Healthy Adult Male Participants

d. the proposed presentation of safety information within the Summary of Clinical Safety (SCS; Module 2.7.4), as outlined in the TOC, is appropriate to support the review of the planned BLA?

FDA response to Question 11: We agree that the proposed presentation of biopharmaceutical and analytical method information and clinical pharmacology information in Modules 2.7.1 and 2.7.2, respectively, is appropriate to support the review of the planned BLA. In addition, we agree with your proposal to present efficacy and safety information in Modules 2.7.4 and 2.7.4, respectively.

Meeting Discussion: No meeting discussion took place.

Question 12: Does the Agency confirm there are no other requirements for this BLA submission and Module 1.9.6 is the appropriate eCTD module location for the agreed iPSP?

FDA response to Question 12: Yes, module 1.9.6 is an appropriate location for other correspondence regarding pediatric exclusivity or study plans. Because this drug product for this indication has an orphan drug designation, you are not required to submit a pediatric assessment.

Meeting Discussion: No meeting discussion took place.

Question 13: Pfizer considers marstacimab an important treatment option for the hemophilia population, in particular Hemophilia B patients, given first option for subcutaneous administration and weight of evidence from the completed Phase 3 cohort. Based on this unmet need and initial results provided, Pfizer plans to include a request for Breakthrough Therapy Designation prior to BLA submission.

Does the Agency agree that the data package outlined will enable a designation of a Breakthrough Therapy?

FDA response to Question 13: You can submit a Breakthrough Therapy Designation request (BTDR) for review. Whether the data is sufficient to enable a designation of Breakthrough Therapy will be assessed after the BTDR is formally submitted to the IND.

Meeting Discussion: No meeting discussion took place.

Question 14: Does the Agency agree that the information provided in the sponsor position assessing the structure and mechanism of action of marstacimab is sufficient for the determination that the product is not the “same” as any approved product for orphan drug exclusivity purposes?

FDA response to Question 14: Yes, the information provided is sufficient to determine the product is not the same as any approved product for orphan drug exclusivity purposes.

Meeting Discussion: No meeting discussion took place.

3.0 ADDITIONAL IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
    - Immunogenicity data: ADA/NAb data and relevant analyses for the 4 Chinese non-inhibitor participants.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential:*

[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description

[8] https://www.fda.gov/media/85061/download

of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further action.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

Presentation slides submitted by the Sponsor.

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.

/s/

CARRIE E DIAMOND
07/24/2023 09:00:16 AM