CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761345Orig1s000

OTHER REVIEW(S)

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

BLA	761345
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Elranatamab
Indication	Multiple Myeloma
Applicant	Pfizer Inc.
Requesting Division	Division of Hematologic Malignancies 2 (DHM2)
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analyst, DILI Team, DHN
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Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Frank A. Anania, MD Director (Acting), OND/DHN
Assessment Date	Jul 23, 2023

Context: Elranatamab (ELB) is a bispecific, monoclonal antibody that binds the cluster of differentiation 3 (CD3) receptor complex on T cells and B cell maturation antigen (BCMA) expressed on multiple myeloma (MM) cells. The dual bindings sites permit ELB to bring T cells in proximity to MM cells for their destruction by T cell activation. Elevations in aminotransferases over three times upper limit of normal were common in the registry trial, and Integrated Safety Summary populations with several meeting ALT and total bilirubin criteria for Hy's Law. Therefore, the Division of Hematologic Malignancies 2 (DHM2) requested the DILI Team's opinion on DILI risk and labeling for hepatotoxicity.

Executive Summary: We do not see a DILI risk that would hold up approval, but Section 5 labeling for liver injury should be considered. Overall, there were three subjects meeting aminotransaminase and bilirubin criteria for Hy's Law out of 187 subjects exposed in the single arm registry trial and five additional subjects meeting such criteria in the ISS population. However, only one subject was assessed as having possible DILI due to ELB; the case was confounded by possible MM involvement of the liver. Even though there were no probable or highly likely Hy's Law cases, elevation in liver enzymes was common, and detection of DILI concurrent with other causes for elevated liver enzymes such as cytokine release syndrome (CRS) would be challenging post-market to assess. Informing prescribers of the rate of liver test abnormalities and diagnostic possibilities in the label would be worthwhile. Other bispecific monoclonal antibodies that bind T cells via CD3 and aimed at other hematologic malignancies are

labeled for hepatotoxicity in warnings and precautions. Our full assessment and recommendations are in Section 5.0.

Consultation Sections:

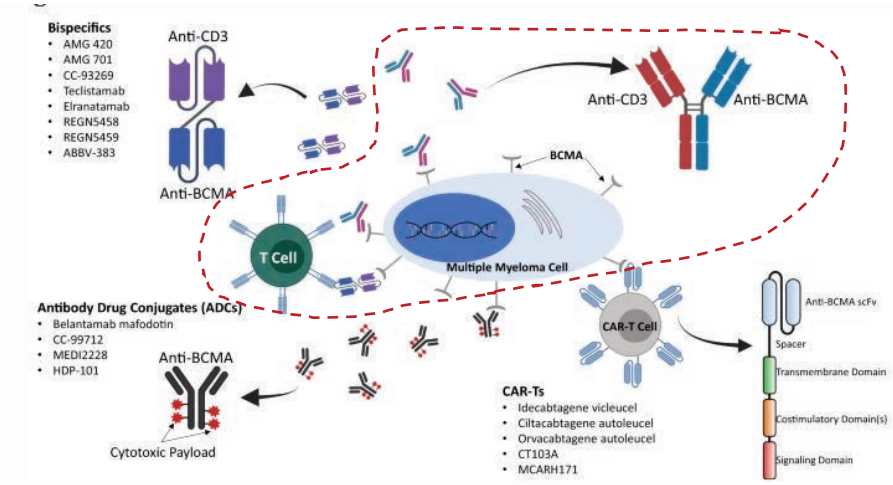
Section 1.0 – Target Disease and Rationale
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.
Appendix 1: Study Schema; ISS hepatocellular scatterplot (eDISH)

Abbreviations:
ADME: absorption, distribution, metabolism, excretion
ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AT: aminotransferase (ALT and/or AST)
BCMA: B-cell maturation antigen
BMA: bispecific monoclonal antibody
BMI: body mass index
CD 3: cluster of differentiation 3
CPK or CK: creatine phosphokinase
CYP: cytochrome P450
DB: direct bilirubin
DDI: drug-drug interaction
DILI: drug-induced liver injury
ELB: elranatamab (aka PF-6863135)
GGT: gamma-glutamyl transferase
HDS: herbal and dietary supplements
IP: investigational product
ISS: integrated safety summary
IV: intravenous
LFLC: lambda free light chain
MRI: magnetic resonance imaging
NCTR: National Center for Toxicological Research
PF-6863135: elranatamab
R-value: ALT/ULN ÷ ALP/ULN
SC: subcutaneous
TB: total bilirubin
US: ultrasound
ULN: upper limit of normal

1.0 Target Disease and Rationale

1.1 Target Disease: Multiple myeloma (MM) is a clonal plasma cell proliferative condition characterized by the abnormal elevation of monoclonal immunoglobulins.[1] Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematologic malignancies. In the United States, there are over 32,000 new cases diagnosed annually, and almost 13,000 patients die of the disease. MM is slightly more common in males than females, and is twice as common in African-Americans compared to Caucasians.[2] Medications including bortezomib, thalidomide, dexamethasone, cyclophosphamide, lenalidomide, carfilzomib, pomalidomide, daratumumab, ixazomib, and elotuzumab are used in major treatment regimens for MM.[2] The exact cause of MM is unknown, although MM is thought to arise from a pre-malignant, asymptomatic phase of clonal plasma cell expansion, commonly referred to as monoclonal gammopathy of undetermined significance.[1]

1.2 Rationale for Drug Use: Elranatamab (ELB) is bispecific monoclonal antibody (BMA) delivered by subcutaneous (SC) injection. It binds the cluster of differentiation 3 (CD3) receptor complex on T cells as well as B-cell maturation antigen (BCMA) expressed on multiple myeloma (MM) cells.[3] Bridging these two cells activates an immune response with T cell activation and lysis of the MM cell.[4] (**Figure 1**)



Agents that target BMCA through a variety of mechanisms. *BCMA* B cell maturation antigen, *CAR-T* chimeric antigen receptor T cell, *scFv* single-chain variable fragment

Figure 1: Immune based therapies targeting BCMA including bispecific agents, antibody drug conjugates and CAR-T cells.[5] Elranatamab mechanism of action is shown in the dotted red lassoed area.

2.0 ADME and DDI data pertinent to DILI

2.1 *Structure*: As a monoclonal antibody, ELB has H and L amino acid chains with half of the molecule aimed at binding CD3 and the other aimed at BCMA. (**Figure 2**)

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[1] Albagoush SA,*et al.* Multiple Myeloma. [Updated 2023 Jan 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023; https://www.ncbi.nlm.nih.gov/books/NBK534764/

[2] Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2022 Aug;97(8):1086-1107. doi: 10.1002/ajh.26590

[3] BLA761345 (761345 - 0033 - (32) - 2023-04-24 - ORIG-1 /Clinical/Response To Information Request) - Introduction (#4)

[4] https://www.pfizer.com/news/press-release/press-release-detail/pfizer-initiates-pivotal-phase-2-magnetismm-3-trial-bcma

[5] Paul B. et al. BCMA-Targeted Biologic Therapies: The Next Standard of Care in Multiple Myeloma Therapy. *Drugs* **82**, 613–631 (2022).

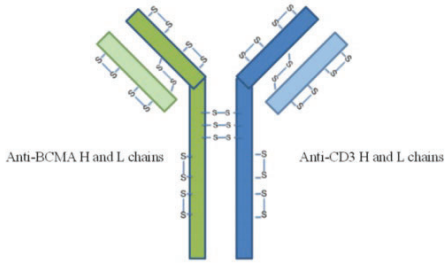

Figure 2: Schematic structure of ELB[6]

2.2 Absorption: Elranatamab (ELB) has a SC bioavailability of 50% in monkeys. Systemic exposure increased dose-proportionally following weekly SC dosing for three months with marked accumulation observed. Steady-state concentrations were reached about six weeks afterwards. Hence, moderate bioavailability and accumulation occurred in monkeys.

2.3 Distribution: Volume of distribution in monkeys was 0.1 L/kg following intravenous (IV) dosing, which was consistent with the limited distribution expected for an immunoglobulin. Non-clinical protein binding and tissue distribution studies were not conducted.

2.4 Metabolism: Standard metabolism studies were not performed because of their limited relevance to antibody agents. ELB is metabolized primarily by catalytic degradation to amino acids and peptides in the vascular and reticuloendothelial system.

2.5 Excretion: The mean half-life following IV dosing ranged from four to six days in monkeys. Standard excretion studies were not conducted because ELB elimination does not follow typical pathways of small molecule, xenobiotic drugs.

2.6: *Drug-Drug Interaction* (*DDI):* No in vitro or in vivo DDI experiments were conducted with ELB. However, ELB increases T-cell activation and induces cytokine production including, for example, interleukin-6 (IL-6). There are in vitro and in vivo data that demonstrate a clear link between elevated IL-6 levels and CYP3A4 suppression, but the changes in vivo rarely lead to significant DDI.[7]

3.0 Non-clinical data

3.1 In vitro data: There were anti-drug antibodies (ADA) following three-month SC and IV experiments in monkeys with an incidence of 33%, 0%, and 0%, respectively at 0.3, 3, and 6 mg/kg/week. The incidence of ADA following one-month repeat, once-weekly dosing in monkeys was about 28% (5/18 monkeys).

3.2 Animal data: In a three-month IV study in monkeys, the LOAEL was 0.3 mg/kg/week with decrease in activity, emesis, soft feces, decrease in body weight, and decrease in food consumption. Moribundity occurred in four of six monkeys at 3 mg/kg/week and six of six at 6mg/kg/week. (The pivotal clinical trial, C1071003, uses a maximum dose of 76 mg SC, weekly.) In the ten-day IV toxicity study, there was a test article related minimal

[6] BLA761345 (761345 - 0033 - (32) - 2023-04-24 - ORIG-1 /Clinical/Response To Information Request) - Introduction (#4)

[7] Kuan-Fu C, et al. Physiologically Based Pharmacokinetic Modeling To Predict Drug-Biologic Interactions with Cytokine Modulators: Are These Relevant and Is Interleukin-6 Enough? *Drug metabolism and Disposition*. 2022, 50(10): 1322-1331. DOI: https://doi.org/10.1124/dmd.122.000926

mononuclear cell infiltration along portal tract in the liver at ≥0.1 mg/kg/dose, with no changes associated in clinical chemistry markers. Minimal, multifocal mononuclear infiltration and mild vacuolation seen in liver occurred in a monkey one-month toxicity study. However, in a three-month weekly dosing, monkey study, there was neutrophilic inflammation and hepatocellular vacuolation, moderate multifocal hepatocyte necrosis, and minimal multifocal mononuclear infiltration. All lobes of the liver were enlarged with minimal to mild pigment deposition. There was an increase in AST up to three times baseline and ALP up to four times baseline in animals euthanized early.

Summary of non-clinical data is in Tables 1 and 2.

Table 1: ADME summary table[8]

Item	Finding
Absorption	Moderate bioavailability
Distribution	Mild to moderate
Metabolism	Catalytic degradation
Elimination	Long half/life

Table 2: Toxicology summary table[9]

Item	Finding
In Vitro Studies	
Major CYPs	N/A
Reaction metabolites (i.e., glutathione trapping)	N/A
Mitochondria studies/inhibition	N/A
Time dependent inhibition (Yes, No, not available)	N/A
LogP	N/A
Covalent binding	N/A
Transporter (BSEP or MRP2 inhibition)	N/A
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Minimal to mild increase in AST and ALP
Liver histopathology findings (animal species)	Mild to moderate inflammation and necrosis

Overall, non-clinical data are mixed and limited. Enzyme changes were minimal but some moderate hepatocyte necrosis occurred in a three-month monkey study. Marked accumulation of drug in monkeys on bioavailability studies and half-life spanning a few days may explain increased liver findings in monkey studies lasting more than a month. In general, immune-mediated DILI tends to have longer latencies and recovery times.

Non-clinical data are limited because BMAs do not produce typical xenobiotic metabolites. Also, there are significant differences in immune tolerance in animals compared to humans. Thus, typical in vitro and animal toxicology studies are less suited to detect liver injury from BMAs. Rather, BMA liver injury may occur by perturbations in the balance between immune tolerance and reactivity, neoantigen formation from

[8] Table made by DILI Team
[9] Table made by DILI Team

peptide byproducts, cross-reactivity with liver cell antigens, or anti-drug antibodies, all of which may be specific to the human liver.

4.0 Clinical data:

4.1 In class or near class data: Our review found six approved bispecific monoclonal antibodies (BMA) that bind T cells via CD3. Three labels mention hepatotoxicity in the Warnings and Precautions sections. (**Table 3**) Teclistabmab can cause hepatotoxicity according to its label with 0.6% exhibiting hyperbilirubinemia and aminotransferase elevations greater than five times ULN (i.e., potential Hy's Law), but there was no mention of hyperbilirubinemia severity. The DILI Team did not review this drug. LiverTox® mentions immune-mediated liver injury with teclistamab in pre-approval trials with one fatality. However, there are no details concerning attribution to teclistamab for these cases in the label or in LiverTox®. All six BMAs have boxed warnings for CRS which can elevate liver enzymes and make detection of DILI challenging.

Table 3: Approved bispecific monoclonal antibodies binding CD3 and DILI information from label and LiverTox®[10]

Drug (Brand), Target Disease	**Antibody Targets**	**Approval year**	**DILI in Warnings/Precautions (W/P, p. 1) and/or Section 5 (S5)**	**DILI Box warning**	**LiverTox® category**[11]
Glofitamab (COLUMVI™) B-cell lymphoma	**CD3,** CD20	2023	No	No	NA
Epcoritamab (EPKINLY™), B-cell lymphoma	**CD3**, CD20	2023	No	No	NA
Teclistamab (TECVAYL™), Multiple myeloma	**CD3**, BCMA*	2022	W/P, p.1 & S5: Yes: recommends monitoring at baseline and as clinically indicated	No	D: possible cause of DILI
Mosunetuzumab (LUNSUMIO™) Follicular lymphoma	**CD3**, CD20	2022	No	No	NA
Tebentafusp (KIMMTRAK®) Uveal melanoma	**CD3**, gp100	2021	W/P, p.1 & S5: Yes; recommends monitoring at baseline and as clinically indicated	No	NA
Blinatumomab (BLINCYTO®), B-cell ALL^	**CD3**, CD19	2014	W/P, p. 1: No S5: Yes; baseline and monitoring and as clinically indicated	No	E*: suspected but unproven cause of DILI

NA = Not available (not yet reviewed)
*B-cell maturation antigen, ^acute lymphocytic leukemia, **Non-small cell lung cancer

[10] Table made by DILI Team upon review of package inserts and LiverTox website
[11] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK547852/

4.1.1 PubMed search: Using the following query "(drug) AND ((hepatotoxicity) or (liver injury) or (DILI))", we found no published cases of DILI in PubMed for the approved bispecific antibodies listed in **Table 3,** but several have been approved only in the last two years.

4.1.2 *The FDA Adverse Events Reporting System (FAERS) data:* The FAERS public dashboard[12] has numerous reports under hepatobiliary reactions for each of the approved agents in **Table 3**. However, many of the cases have other reactions such as CRS included with the hepatobiliary reaction and/or are attributed to multiple drugs besides the bispecific monoclonal antibody. There are no causality assessment data. Therefore, we used the following criteria to maximize specificity for potential DILI events. To be included in **Table 4**, the case must have (a), and (b) or (c) or both below.

a) The BMA is the only drug named in the suspected product field.
and
b) Liver injury, DILI, or hepatotoxicity are without other liver related reactions in the case reaction field.
or
c) Acute/fulminant liver/hepatic failure is without a non-DILI explanation (e.g., hepatitis B) in the case reaction field.

Table 4: Number of cases and reactions reported in FAERS and meeting criteria in 4.1.2 above for BMAs binding CD3 T cells

Drug (Brand)	Number of cases meeting criteria	Count by hepatobiliary reaction type
Glofitamab,(COLUMVI™)	0	NA
Epcoritamab (EPKINLY™)	0	NA
Teclistamab, (TECVAYL™)	1	1: Hepatitis fulminant/acute hepatic failure/Covid-19 Pneumonia
Mosunetuzuma, (LUNSUMIO™)	0	NA
Tebentafusp, (KIMMTRAK®)	1	1: Hepatotoxicity
Blinatumomab, (BLINCYTO®)	26	2: DILI 21: Hepatotoxicity* 3: Liver injury

*Includes two with venoocclusive disease

Blinatumomab has the most cases with hepatobiliary reactions reported to FAERS, but it has also been on the market the longest by seven to nine years. Also, criteria used in 4.1.2 are stringent and may underestimate hepatotoxicity cases.

4.2 Study protocol(s): Five studies completed, or ongoing are listed in this BLA: two phase 1 studies; two phase 1b/2 studies (one ongoing); one phase 2; and one phase 3 that is ongoing.[13] All studies are open label without placebo or non-ELB therapy arms, except for the phase 3 study which has a daratumumab plus pomalidomide arm. The phase 3 study (C1071005) has a 90-day safety update consisting of narratives, none of which contain liver related MeDRA preferred terms. No phase 3 study datasets or

[12] FAERS public dashboard https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis
[13] BLA761345 (761345 - 0006 - (21) - 2023-03-16 - GI-1 /General Correspondence) - Tabular listing

clinical safety reports are available. As suggested in DHM's consult request, we focused on the completed pivotal phase 2 study, C1071003, though we also analyzed data from the integrated safety summary (ISS) dataset.

4.2.1 *Study C1071003*: *An Open-Label, Multicenter, Non-randomized Phase 2 Study of Elranatamab (PF-6863135) Monotherapy in Participants with Multiple myeloma Who are Refractory to at Least One Proteasome Inhibitor, One Immunomodulatory Drug and One Anti-CD38 Antibody*. The study had 187 subjects, split into Cohort A (123 subjects) who were naïve to prior BCMA-directed therapy and Cohort B (64 subjects) who had been treated with BCMA-directed agents. The protocol excluded subjects with aminotransferases >2.5x ULN or TB > 2x ULN (exception: Gilbert's Syndrome). There were no other inclusion or exclusion criteria pertinent to the liver or DILI risk. All subjects received ELB subcutaneously (SC) with gradually increased doses during the first week (Cycle one). The starting dose was 12 mg followed by 32 mg by day four, and then 76 mg by Day 8 (start of Cycle two). After at least six cycles, the dose frequency was reduced from weekly to biweekly if at least partial response criteria were met. If response criteria were not met or if disease progressed at any time, the dose stayed constant or frequency was increased to weekly. Therapy continued until "confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination."[14] Study schematic is in the **Appendix**.

4.3 Study level data

4.3.1 *Study C1071003*: Elevation liver enzymes over 3x ULN were common at approximately 11% for ALT, AST, or AP. (**Table 5**) Three subjects fell in the potential Hy's Law quadrant on hepatocellular scatterplot or eDISH (**Figure 3**), but only one was considered possible DILI due to ELB. (See section 4.4 for case level analyses) This subject (b) (6) also had ALP elevation localizing to the right upper quadrant in the cholestatic scatterplot. The subject in the cholestasis quadrant on eDISH remained in the left upper quadrant of the cholestatic plot indicating no ALT, AST or ALP elevation accompanying jaundice making cholestatic DILI unlikely. All subjects received ELB at dosing outlined in 4.2.1 above.

[14] BLA761345 (761345 - 0006 - (21) - 2023-03-16 - GI-1 /General Correspondence) - C1071003 - Protocol (#20)

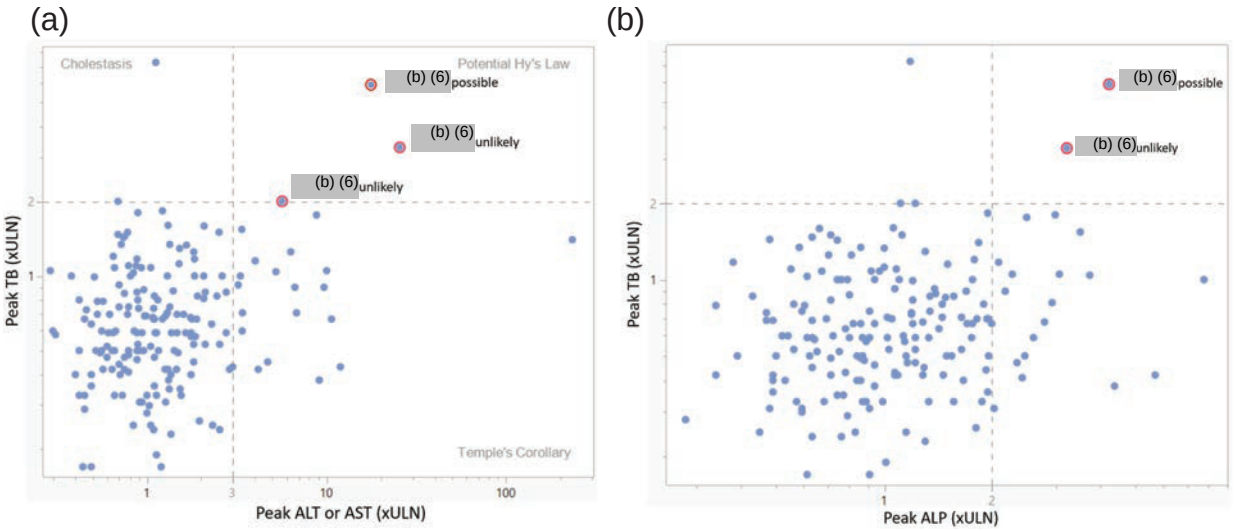

Figure 3: Study C1071003 subjects (N=187) by (a) hepatocellular scatterplot (eDISH) and (b) cholestatic scatterplot. Subjects in the right upper quadrants are identified by subject ID and DILI likelihood category.

Table 5: Proportions of subjects in Study C1071003 with peak ALT, AST, and ALP levels at designated multiples of ULN. (N=187)

ALT Elevations	**Elevation Count**	**%**
Less than 3x ULN	166	88.8%
Between 3x and 5x ULN	12	6.4%
Between 5x and 10x ULN	6	3.2%
Between 10x and 20x ULN	2	1.1%
20x ULN or Greater	1	0.5%
AST Elevations		
Missing Test Result	2	1.1%
Less than 3x ULN	166	88.8%
Between 3x and 5x ULN	8	4.3%
Between 5x and 10x ULN	6	3.2%
Between 10x and 20x ULN	3	1.6%
20x ULN or Greater	2	1.1%
AP Elevations		
Less than 2x ULN	167	89.3%
Between 2x and 3x ULN	12	6.4%
3x ULN or Greater	8	4.3%

4.3.2 *Integrated Safety Summary (ISS) dataset*. The ISS hepatocellular scatterplot (eDISH) revealed five additional cases in the potential Hy's Law quadrant. (**Appendix**) Though narratives were not available, safety reports and laboratory values including liver analytes with line graphics were analyzed. All five were assessed as unlikely DILI due to latencies of over one year (two subjects), or a competing diagnosis of CRS, tumor lysis syndrome or disease progression (three subjects). All five subjects had substantially higher AST compared to ALT, high LDH levels and/or high urate levels.

4.4 Case level analyses

4.4.1 *Summary of cases*: On detailed assessment of the three subjects from Study C1071003 in Hy's Law quadrant, we considered two unlikely and one possible DILI due to ELB. (**Table 6**)

Table 6: DILI likelihood category, age, sex, and lab values for three subjects in the Potential Hy's Law quadrant of Study C1071003 hepatocellular scatterplot (eDISH)[15]

ID	Causality Score*	Alternate diagnosis	Study	Age (yr)	Sex	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak**
(b) (6)	4	MM in liver	C1071003	62	F	No	50	7	586	435	201	5.9	8.9
	5	CSR	C1071003	71	F	No	1	[252]	210	201	144	2.4	4.5
	5	Hemolysis	C1071003	64	F	No	25	[84]	372	998	231	3.3	4.9

MM = multiple myeloma; CSR = cytokine release syndrome

R-value = (ALT/ULN) ÷ (AP/ULN); R ≥ 5: hepatocellular; R between 2 & 5 mixed; R ≤ 2 cholestatic

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

~[ ] day values means the drug continued for that many days *after* injury onset.

4.4.2 Detailed discussion of Study C1071003 cases falling in Hy's Law quadrant

1. *Subject* (b) (6)*: **Possible** DILI due to ELB.*

Summary: This is a 62-year-old woman with MM who had elevation in transaminases and jaundice seven weeks after starting ELB.

Her BMI was 19.9 kg/m^2; she had an "ongoing history of LFT increased" but at baseline her ALT was 48 U/L, AST 33 U/L, ALP 112 U/L and TB 0.41 mg/dL. Her lambda free light chain (LFLC) level was high at 3737.6 mg/L (Normal: <26 mg/L). She was on allopurinol (start (b) (6) Day -36), rasburicase, a recombinant urate oxidase for hyperuricemia (start (b) (6); Day 22). There were no other concomitant medications pertinent to DILI risk.

She started ELB on (b) (6) (Day 1) at 12 mg followed by 32 mg on (b) (6) (Day 4), and 76 mg on (b) (6) (Day 8), with weekly dosing thereafter. On (b) (6) (b) (6) (Day 30), her LFLC was higher at 19,366 mg/L. Last dose of ELB before laboratory tests abnormalities noted was (b) (6) (Day 44). On (b) (6) (Day 51), ALT was 528 U/L, AST 501 U/L, AP 195 U/L and TB 1.4 mg/dL. LDH was also elevated at 829 U/L. ELB administration was stopped and allopurinol was continued. On (b) (6) (Day 58), LFLC was lower at 12,291 mg/L. Aminotransferases were lower at ALT 459 U/L and AST 236 U/L; AP was higher at 433 U/L, TB was 5.9 mg/dL and LDH 665 U/L. On Day 61, extramedullary multiple myeloma was noted in the liver with bilateral pleural effusions on MRI, but no liver biopsy was mentioned. No evaluation testing was done. At last follow-up, TB was still elevated but AST had fallen by >50%, six days after peak. (**Figure 4**) There was no mention of symptoms like fever, rash, or pruritus.

[15] Table made by DILI Team

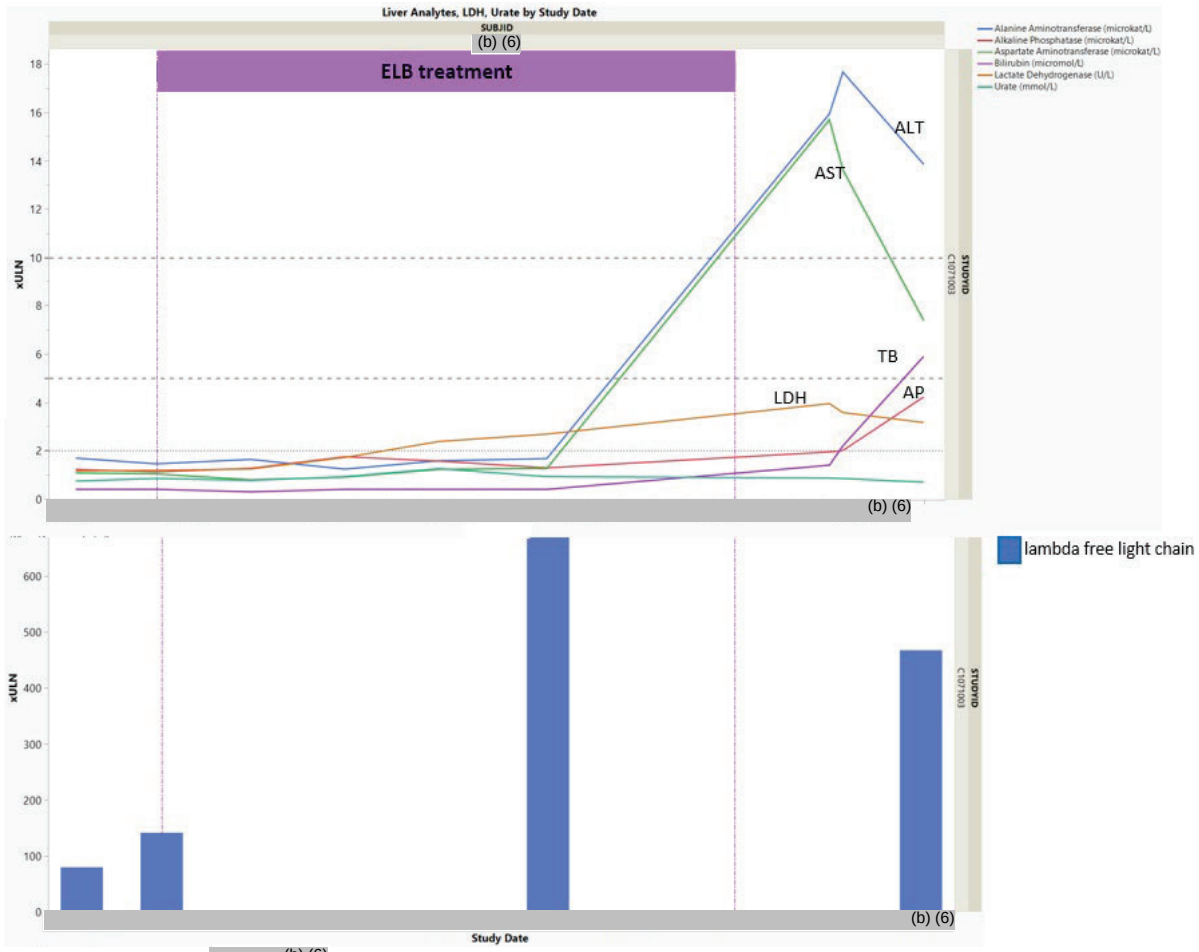

Figure 4: Subject (b) (6) liver analytes, LDH, urate (lines) and lambda free light chain (bars) levels in x ULN by study date.[16]

Assessment: This case is complex, and we assessed it as possible DILI due to ELB. Latency and initial dechallenge fit well with DILI. However, the subject also had extramedullary disease (EMD) in the liver by MRI and markedly high LFLC levels, so EMD related liver injury competes. LFLC levels increased by nine-fold between screening and day 51, but then fell by 36% (19K to 12K mg/L) as liver enzymes were also falling during dechallenge. Such high LFLC levels would be in the upper tertile according to one study of 300 MM patients and would be consistent with advanced or aggressive disease.[17] A fall in LFLC would also be consistent with a therapeutic response. New liver parenchymal findings on MRI and LDH of >800 U/L when the ALT peaked at only 528 U/L are atypical of DILI alone. Therefore, the possibility of EMD in the liver must be considered despite lack of histologic confirmation. No evaluation testing was done, so viral infections (hepatitis A, B, CMV, EBV etc.) still compete. DILI due to ELB may have been concurrent with these other possibilities. Allopurinol continued even as liver enzymes fell so it is less likely causal. Rasburicase can cause

[16] Made by DILI Team using JMP 16.0
[17] van Rhee, F, et al. High serum-free light chain levels and their rapid reduction in response to therapy define an aggressive multiple myeloma subtype with poor prognosis. *Blood*. 2007; 110:827-32.

DILI but usually with hypersensitivity manifestations and short latency (less than a few days), neither of which were present in this case.

2. *Subject* (b) (6): ***Unlikely*** *DILI due to ELB*

Summary: This is a 64-year-old woman with elevated liver enzymes and jaundice 25 days after ELB start.

At baseline, ALT, AST, AP, and TB were 16 U/L, 19 U/L, 423 U/L and 1.57 mg/dL, respectively. LDH was 90 U/L. BMI 25.9 kg/m^2. Based on her medication, she had bone density loss but no other chronic medical illnesses. There were no concurrent medications pertinent to DILI risk.

On (b) (6) (Day 1), she started ELB at 12 mg. She did not receive doses on Days 5 or Day 9 due to blood dyscrasias. On (b) (6) (Day 16), she received 32 mg.

On (b) (6) (Day 25), her ALT, AST, AP, TB and LDH were 102 U/L, 128 U/L, 191 U/L and 2.28 mg/dL (no fractionation provided) and 339 U/L respectively. By (b) (6) (Day 32), ALT, AST and LDH were up to 372 U/L, 998 U/L and 1967 U/L respectively. AP and TB peaked at 231 U/L and 3.27 mg/dL. Scheduled dose for Day 33 was held. Bone marrow and PET/CT were negative for disease progression. Oral dexamethasone was given (40 mg/d x 4 days). Thereafter, liver analytes fell quickly, (**Figure 5**) and ELB was restarted on (b) (6) (Day 40) at the previous 76 mg dose without further issues through (b) (6) (Day 110). Serologies for hepatitis A, B and C were negative. CMV PCR was negative. No other evaluation testing was mentioned.

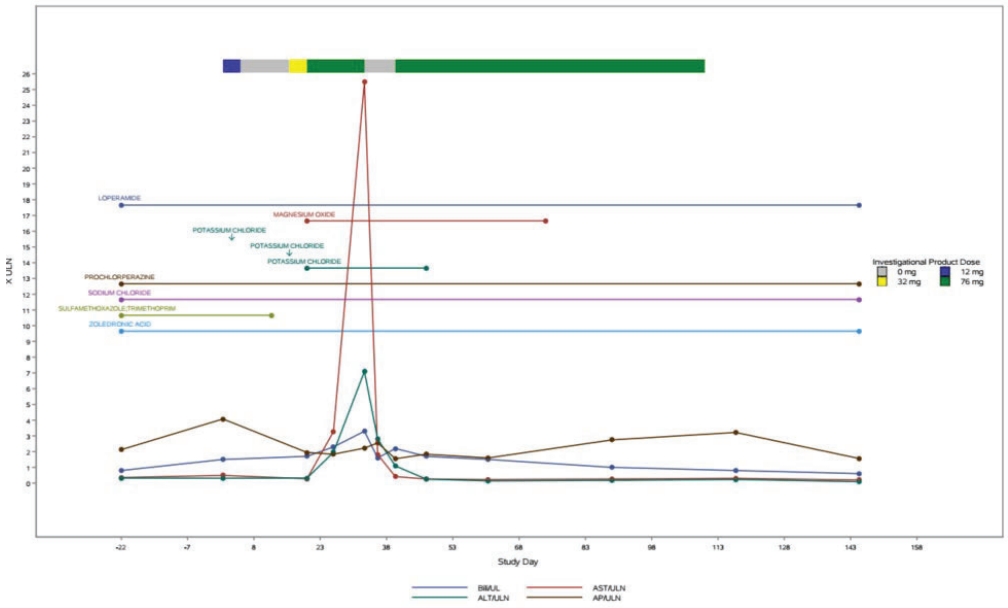

Figure 5: Subject (b) (6) liver analyte levels and ELB exposure by study day[18]

Assessment: We assessed this case as unlikely DILI due to ELB. LDH was 1967 U/L and AST was markedly higher than ALT, so tumor lysis or hemolysis competes. Rapid fall in enzymes and negative rechallenge are also inconsistent with DILI.

3. *Subject* (b) (6): ***Unlikely*** *due to ELB*

[18] BLA761345 (761345 - 0033 - (32) - 2023-04-24 - ORIG-1 /Clinical/Response To Information Request) - C1071003 - Figure 14.3.4.3.2 Plot of Liver Biochemistries in Multiples of ULN by Study Day with Study Treatment and Other Concomitant Drug Treatment - 10071003

Summary: This is a 71-year-old woman with MM who had elevation in aminotransferases with jaundice starting one day after taking ELB.

Her BMI was 27.6 kg/m^2. Her medical history included coronary artery disease, hypertension, and hyperlipidemia. Concurrent medications included pravastatin since (b) (6) (month and date not provided) and no other medications pertinent to DILI. Her ALT, AST, AP, and TB levels were 10 U/L, 13, U/L, 109 U/L and 0.4 mg/dL respectively.

She started ELB 12 mg SC on (b) (6) (Day 1). The next day she had fever (39.3^o C) with rigors, and her ALT increased to 52 U/L and AST 116 U/L. Grade 1 CRS was diagnosed. She continued to have fever with rising liver enzymes that would peak on (b) (6) (Day 3), at ALT of 210 U/L, AST 201 U/L, AP 144 U/L and TB 2.4 mg/dL (R-value 4.5). Thereafter, her liver tests fell by 50% in one to two days and back to normal in seven days. (**Figure 6**) On (b) (6) (Day 5), she was also diagnosed with E. coli enteritis. However, by (b) (6) (Day 7), she had improved, and her CRS resolved. She received 32 mg of ELB that day. She tolerated doses of 44 mg and 76 mg over the next several months without liver enzyme elevations. No evaluation testing was reported.

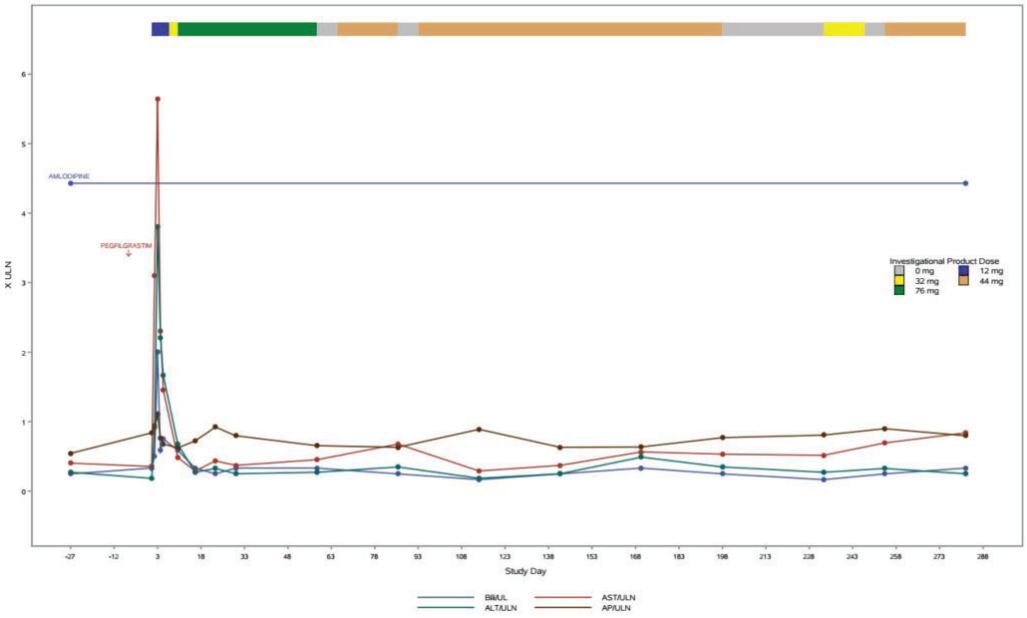

Figure 6: Subject (b) (6) liver analyte levels and ELB exposure by study day[19]

Assessment: We assessed this case as unlikely DILI due to ELB. Latency was quick and the subject had fever and rigors, all of which are more consistent with CRS. There was also negative rechallenge with no liver issues with continued dosing for over 250 days.

5.0 Assessment & Recommendations

[19] BLA761345 (761345 - 0033 - (32) - 2023-04-24 - ORIG-1 /Clinical/Response To Information Request) - C1071003 - Figure 14.3.4.3.1 Plot of Liver Biochemistries in Multiples of ULN by Study Day with Study Treatment and Other Concomitant Drug Treatment - 10031016

5.1 Assessment: Elranatamab (ELB) is a bispecific monoclonal antibody (BMA) that binds the cluster of differentiation 3 (CD3) receptor complex on T cells and B cell maturation antigen (BCMA) expressed on MM plasma cells. The dual bindings sites permit ELB to bring T cells next to MM cells for their destruction by T cell activation. Several subjects in the single registry trial and integrated safety summary (ISS) population had liver biochemistry elevations suggesting Hy's Law qualification, and the Division of Hematologic Malignancies (DHN) consulted the DILI team regarding hepatotoxicity risk and need for hepatotoxicity labeling.

The non-clinical data revealed mild to modest risk for DILI, but data are limited. Lack of xenobiotic metabolite formation and differences in immune tolerance between species, make typical in vitro and animal toxicology studies insensitive to detecting liver injury from bi-specific monoclonal antibodies. Liver injury may occur via creating imbalances between immune tolerance and reactivity, neoantigen formation from peptide byproducts, cross-reactivity with liver antigens, or anti-drug antibodies, all of which may be specific to the human immune system. Thus, DILI from monoclonal antibodies is likely immune mediated and unpredictable. Marked accumulation of drug in monkeys on bioavailability studies and half-life spanning a few days are noteworthy and could delay or prolong hepatotoxicity should it occur. In general, immune mediated DILI is believed to have longer latencies and recovery times.

Study level data analyses was limited to one study with only active arms and the ISS which also lacked placebo or comparator treatment arms. Therefore, comparative analysis was not possible. In Study 1071003, elevation in aminotransferases over three times ULN was common, and three of 187 subjects exposed to ELB had jaundice (TB >2x ULN) thus meeting aminotransferase and TB criteria for Hy's Law. Analysis of the ISS revealed five additional subjects meeting these biochemistry criteria for Hy's Law.

On case level analyses, only one was considered possible DILI due to ELB, while the other seven were considered unlikely. The case of possible DILI was confounded by possible extramedullary disease in the liver. Therefore, we were unable to confirm a severe DILI risk in this NDA, though the number exposed was small. None of the six approved BMAs that bind CD3 we identified have boxed warnings for hepatotoxicity, but three have it in the label's Warnings and Precautions. All six have boxed warnings for CRS which can make a diagnosis of DILI difficult. The FAERS public dashboard contains hepatobiliary reactions for all the BMAs but specificity for true DILI is not clear from our limited analyses of these post-market data.

Thus, the NDA data do not support a hepatotoxicity risk that should hold up approval, particularly for MM patients who have failed other therapies and are in dire need of treatment. While we do not suggest a boxed warning, including hepatotoxicity in the warnings and precautions section should be considered because of the subject with possible significant DILI, frequent elevation of liver analytes in their registry study and ISS populations, and other BMAs labeled for hepatotoxicity suggesting a possible class effect. Detection of DILI concurrent with other causes for elevated liver enzymes such as CRS will be challenging in the post-market setting. Informing prescribers of the rate

of liver test abnormalities and diagnostic possibilities in the label would be helpful. Also, ELB was not studied in those with baseline aminotransferases over 2.5x ULN and/or TB >2x ULN, so safety in patients with such elevations at baseline is unknown and stating this uncertainty in the label should be considered. We recommend the label advise against using ELB in subjects with acute or unstable chronic liver disease or decompensated cirrhosis. Checking baseline liver tests with later checks as clinically indicated would also be prudent.

Routine pharmacovigilance is suggested. The need for more involved post-market research such as cohort or registry studies is not supported by the data.

5.2 Recommendations

1) Do not hold up approval for liver injury risk
2) Labeling recommendations:
    a. No box warning for hepatotoxicity needed.
    b. Consider hepatotoxicity in Warnings and Precautions with Section 5 description of liver analyte elevation rates and potential causes.
    c. Recommend baseline liver analyte checks and as clinically indicated thereafter.
    d. Consider stating that liver safety for patients with aminotransferases >2.5x ULN and/or TB >2x ULN are lacking.
    e. Exclude patients with unstable chronic liver disease, acute liver disease or decompensated cirrhosis.
3) Routine pharmacovigilance.

Ling Lan -S
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Date: 2023.07.26 10:25:50 -04'00'

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, DHN
CDER/OND

Paul H. Hayashi -S
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Paul H. Hayashi, MD, MPH
DILI Team Lead, DHN
CDER/OND

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Date: 2023.07.26 13:11:42 -04'00'

Frank A. Anania, MD
Director (Acting), DHN
CDER/OND

Appendix:

Figure A: Study 1071003 schema[20]

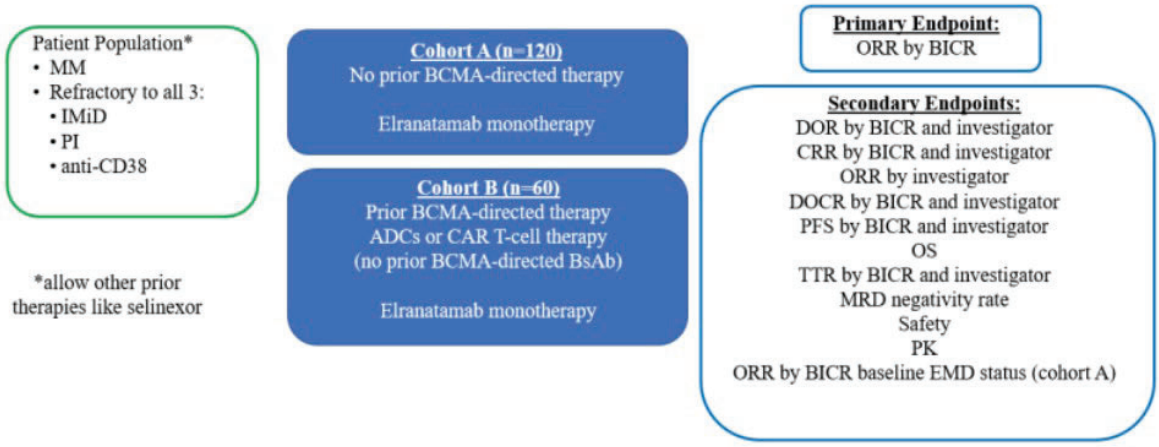
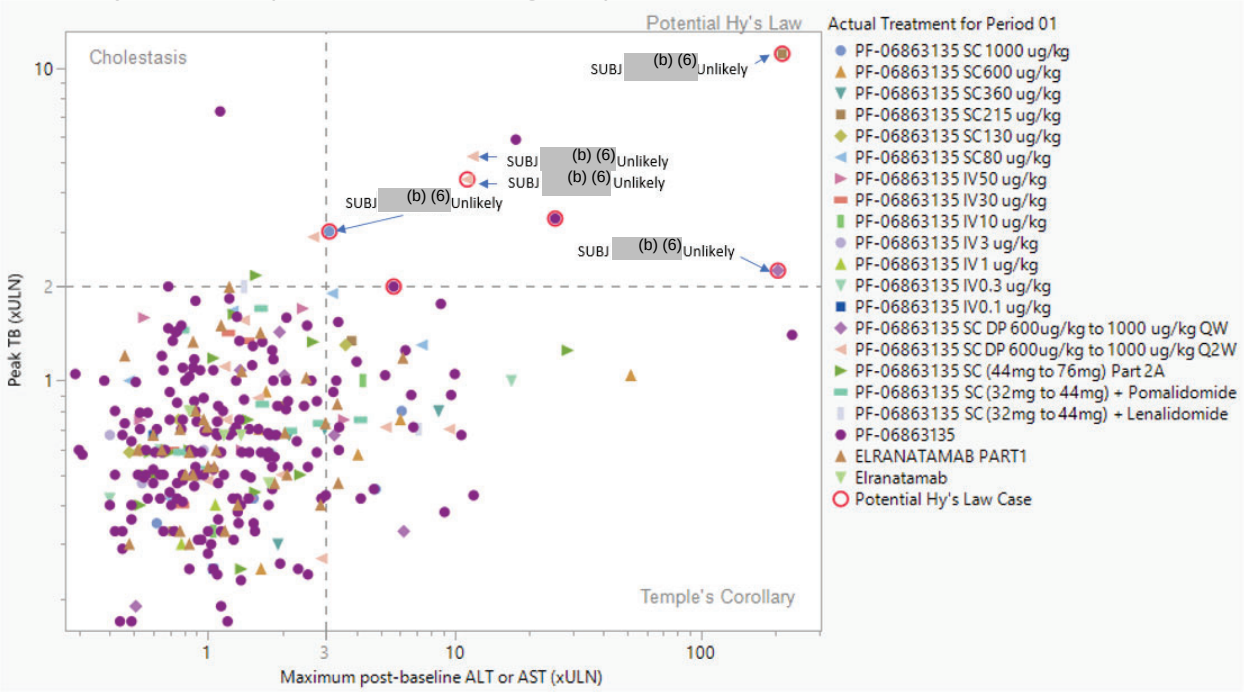


Figure B: Integrated Safety Summary (ISS) hepatocellular scatterplot (eDISH). Five subjects in Potential Hy's Law quadrant identified by Subject ID and DILI likelihood category. Three unidentified subjects are from Study C1071003 (See Section 4.3.1, **Figure 3**)[21]



[20] BLA761345 (761345 - 0006 - (21) - 2023-03-16 - GI-1 /General Correspondence) - C1071003 - Protocol (#21)

[21] Made by DILI Team using JMP Clinical 8.1

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/s/

PAUL H HAYASHI
07/27/2023 09:48:10 AM

Office of Prescription Drug Promotion

Internal Consult

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

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Kate Oswell, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Melissa Khashei, Regulatory Review Officer, OPDP

CC: Jina Kwak, Team Leader, OPDP
Wana Manitpisitkul, Safety Regulatory Project Manager, OSE
Naomi Boston, Team Leader, DRM
Robert Pratt, Risk Management Analyst, DRM
Laura Zendel, Associate Director for REMS Design and Evaluation, DRM
Michael Wade, OPDP
CDER-OPDP-RPM

Date: July 27, 2023

Re: BLA 761345
ELREXFIO™ (elranatamab-bcmm) injection, for subcutaneous use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

---

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for ELREXFIO:

- Healthcare Provider (HCP) REMS Materials:
  - ELREXFIO REMS Healthcare Provider Letter
  - ELREXFIO REMS Professional Society Letter
  - ELREXFIO REMS Factsheet
  - ELREXFIO REMS Knowledge Assessment
  - ELREXFIO REMS Adverse Reaction Management Guide
  - ELREXFIO REMS Prescriber Enrollment form
  - ELREXFIO REMS Pharmacy and Healthcare Setting Enrollment Form
  - ELREXFIO REMS Prescriber Training Program
  - ELREXFIO REMS Pharmacy and Healthcare Setting Training

- Direct-to-Consumer (Patient) REMS Materials:
  - ELREXFIO REMS Patient Wallet Card

- ELREXFIO REMS Website

The version of the draft REMS materials used in this review were sent from DRM by Kate Oswell via email on July 14, 2023. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for ELREXFIO.

General Comment

Please remind Pfizer that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.ELREXFIOREMS.com and toll-free number 1-844-923-7845. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Pfizer that the REMS specific website should not be the sole source of approved REMS materials.

The versions of the proposed draft Prescribing Information (PI) entitled "Annotated_USPI-elranatamab-solution for injection- 40 mg per mL_Pfizer_7.18.23," and the proposed draft Medication Guide (MG), entitled "Annotated_Med Guide-elranatamab-solution for injection- 40 mg per mL_Pfizer 7.18.23" used for review were obtained from DRM (Kate Oswell) on July 19, 2023, and are attached to the end of this review. OPDP's comments are based on this version of the draft labeling and the REMS materials should be updated, as needed, based on the final approved labeling.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see "Specific Comment[s]" below):

- ELREXFIO REMS Healthcare Provider Letter
- ELREXFIO REMS Professional Society Letter
- ELREXFIO REMS Prescriber Enrollment form
- ELREXFIO REMS Pharmacy and Healthcare Setting Enrollment Form
- ELREXFIO REMS Pharmacy and Healthcare Setting Training
- ELREXFIO REMS Website

Specific Comment[s]

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:

ELREXFIO REMS Fact Sheet

- Pages one and two of the ELREXFIO REMS Fact Sheet include a section titled, "How Can Healthcare Providers Manage the Risks?"
  - **Risk**
    - This presentation minimizes risks by omitting material information. The WARNINGS AND PRECAUTIONS, *Neurologic Toxicity including ICANS* section of the draft PI states, "Advise patients not to drive or operate heavy or potentially dangerous machinery for 48 hours after completing each of the 2 step-up doses and the first treatment dose within the ELREXFIO step-up dosing schedule and in the event of new onset of any neurological toxicity symptoms until symptoms resolve." Therefore, OPDP recommends revising this presentation to include this material information.

- Pages one and two of the ELREXFIO REMS Fact Sheet include the following sections:
  - "ELREXFIO REMS Overview"
  - "Key Requirements of the ELREXFIO REMS."
    - **Risk**
      - These presentations omit material information regarding the requirements of the ELXREXFIO REMS. The WARNINGS AND PRECAUTIONS, *ELREXFIO REMS* section of the draft PI states, "Prescribers must counsel patients receiving ELREXFIO about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with ELREXFIO Patient Wallet Card." Therefore, OPDP recommends revising these presentations to include this material information.

ELREXFIO REMS Knowledge Assessment

- Pages three and four of the **ELREXFIO REMS Knowledge Assessment** include the following question and answer options:

  "If CRS is suspected during treatment with ELREXFIO, which of the following supportive measures should be considered:

  A. Withhold ELREXFIO until Grade 1 or Grade 2 and Grade 3 (first occurrence) CRS resolves
  B. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS
  C. Laboratory testing for pulmonary, cardiac, renal, and hepatic function
  D. All of the above"

  - **Risk**

    Answer choice C is inconsistent with the DOSAGE AND ADMINISTRATION, *Dosage Modifications for Adverse Reactions* section of the draft PI which states, "Consider laboratory testing to monitor for **disseminated intravascular coagulation (DIC), hematology parameters**, as well as pulmonary cardiac, renal, and hepatic function" (bolded emphasis added).

ELREXFIO REMS Adverse Reaction Management Guide

- Page one of the ELREXFIO REMS Adverse Reaction Management Guide includes the statement, "If CRS is suspected, withhold ELREXFIO until the CRS resolves."
  - **Risk**
    - This presentation minimizes risks by omitting material information. The WARNINGS AND PRECAUTIONS, *Cytokine Release Syndrome* section of the draft PI states (bolded emphasis added):

      Clinical signs and symptoms of CRS may include, but are not limited to, fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes.

      At the first sign of CRS, evaluate patients immediately for hospitalization. Manage CRS according to the recommendations and consider further management per current practice guidelines. **Withhold or permanently discontinue ELREXFIO based on severity**"

      Therefore, OPDP recommends revising this presentation to include this material information.

- Page three of the ELREXFIO REMS Adverse Reaction Management Guide includes the statement, “At the first sign of neurologic toxicity including ICANS withhold ELREXFIO…”
  - **Risk**
    - This presentation minimizes risks by omitting material information. The WARNINGS AND PRECAUTIONS, *Neurologic Toxicity, Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)* section of the draft PI states (bolded emphasis added):

      The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

      At the first sign of neurologic toxicity, including ICANS, evaluate and treat patients **immediately based on severity. Withhold or permanently discontinue ELREXFIO based on severity per recommendations** [see Dosage and Administration (2.5)] and consider further management per current practice guidelines

      Due to the potential for neurologic toxicity including ICANS, patients receiving ELREXFIO are at risk of depressed level of consciousness. Advise patients not to drive or operate heavy or potentially dangerous machinery for 48 hours after completing each of the 2 step-up doses and the first treatment dose within the ELREXFIO step-up dosing schedule and in the event of new onset of any neurological toxicity symptoms until symptoms resolve.”

      Therefore, OPDP recommends revising this presentation to include this material information.

ELREXFIO REMS Prescriber Training Program

- Slide nine of the ELREXFIO REMS Prescriber Training Program includes information regarding the Boxed Warning for ELREXFIO.
  - **General Comment**
    - This presentation is inconsistent with the language used in the BOXED WARNING section of the draft PI. We recommend revising this presentation to maintain consistency with the draft PI.

- Slide 15 of the ELREXFIO REMS Prescriber Training includes information about neurologic toxicity rates in the clinical trial.
  - **Risk**
    - This presentation omits material information regarding the risks the ELREXFIO. The WARNINGS AND PRECAUTIONS, *Neurologic Toxicity, Including (ICANS)* section of the draft PI states, “In the clinical trial, neurologic toxicity occurred in 59% of patients who

received ELREXFIO at the recommended dosing schedule [see Dosage and Administration (2.2)], **with Grade 3 or 4 neurologic toxicity occurring in 7% of patients. Neurologic toxicities included headache (18%), encephalopathy ((b) (4)%), motor dysfunction ((b) (4)%), sensory neuropathy (13%), and Guillain-Barré Syndrome (0.5%)**" (bolded emphasis added). Therefore, OPDP recommends revising this material information.

ELREXFIO REMS Patient Wallet Card

- Page one of the ELREXFIO REMS Patient Wallet Card includes a list of symptoms under the heading, "Call your healthcare (b) (4) or get emergency help right away if you (b) (4) any of these symptoms:"
  - **General Comment**
    - This presentation is inconsistent with the symptoms listed in the **What is the most important information I should know about ELXREXFIO?** *Cytokine Release Syndrome (CRS) and Neurologic problems* sections of the draft MG. We recommend revising this presentation to maintain consistency with the draft MG.

- Page one of the ELREXFIO REMS Patient Wallet Card includes the heading, "FOR THE PATIENT"
  - **Risk**
    - This presentation minimizes risks by omitting material information. The **What is the most important information I should know about ELREXFIO?** section of the draft MG states, (b) (4) Therefore, OPDP recommends revising this presentation to include this material information.

- Page one of the ELREXFIO REMS Patient Wallet Card includes the following statement, (b) (4) (bolded emphasis original, underlined emphasis added).
  - **Risk**
    - This presentation is inconsistent with information in the draft PI. The **What is the most important information I should know about ELREXFIO?** section of the draft MG states, "**Due to the risk of CRS**, you will receive ELREXFIO on a 'step-up dosing schedule' and should be hospitalized for 48 hours after the first 'step-up' dose and for 24 hours after the second 'step-up' dose of ELREXFIO" (bolded emphasis original, underlined emphasis added).

We recommend revising this presentation to maintain consistency with the draft MG.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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MELISSA KHASHEI
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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: 7/10/23

To: Natasha Kormanik, MSN, CRNP, FNP-BC, OCN
Senior Regulatory Health Project Manager
Division of Hematologic Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELREXFIO (elranatamab-bcmm) injection, for subcutaneous use

BLA: 761345

Background:
In response to DHM2's consult request dated January 11, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for ELREXFIO (elranatamab-bcmm) injection, for subcutaneous use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on June 29, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on July 6, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on June 29, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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JENNIFER W CHEN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 07, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761345
Product Name, Dosage Form, and Strength:	Elrexfio (elranatamab-bcmm) Injection, 76 mg/1.9 mL (40 mg/mL) and 44 mg/1.1 mL (40 mg/mL)
Applicant/Sponsor Name:	Pfizer, Inc.
TTT ID #:	2022-3129-2
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 28, 2023 for Elrexfio. We reviewed the revised container labels and carton labeling for Elrexfio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

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

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[a] Topper, C. Label and Labeling Review Memo for Elrexfio (BLA 761345). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUN 16. TTT ID No.: 2022-3129-1.

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/s/

CHRISTINA A TOPPER
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HINA S MEHTA
07/10/2023 03:55:11 PM

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:	July 6, 2023
To:	Natasha Kormanik, MSN, CRNP, FNP-BC, OCN® Regulatory Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ELREXFIO (elranatamab-bcmm)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761345
Applicant:	Pfizer Inc.

1 INTRODUCTION

On December 19, 2022, Pfizer Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761345 for ELREXFIO (elranatamab-bcmm) injection, with a proposed indication for the treatment of relapsed or refractory multiple myeloma (RRMM).

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 Hematologic Malignancies II (DHM2) on January 11, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ELREXFIO (elranatamab-bcmm) injection.

2 MATERIAL REVIEWED

- Draft ELREXFIO (elranatamab-bcmm) injection MG received on December 19, 2022 and received by DMPP and OPDP on June 29, 2023.
- Draft ELREXFIO (elranatamab-bcmm) injection Prescribing Information (PI) received on December 19, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 29, 2023.
- Approved COLUMVI (gloflitamab-gxbm), EPKINLY (epcoritamab-bysp), LUNSUMIO (mosunetuzumab-axgb), and TECVAYLI (teclistamab-cqyv) comparator labeling dated June 15, 2023, May 19, 2023, December 22, 2022, and October 25, 2022, respectively.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

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07/06/2023 12:36:15 PM

JENNIFER W CHEN
07/06/2023 02:24:25 PM

LASHAWN M GRIFFITHS
07/06/2023 02:41:08 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 16, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761345
Product Name, Dosage Form, and Strength:	Elrexfio (elranatamab-bcmm) Injection, 76 mg/1.9 mL (40 mg/mL) and 44 mg/1.1 mL (40 mg/mL)
Applicant/Sponsor Name:	Pfizer, Inc.
TTT ID #:	2022-3129-1
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 14, 2023 for Elrexfio. We reviewed the revised container labels and carton labeling for Elrexfio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The carton labeling does not include how the medication guide is provided. The manufacturer information competes in prominence with critical product information.

3 RECOMMENDATIONS FOR PFIZER, INC.

We recommend the following be implemented prior to the approval of BLA 761345:

A. Container label and Carton Labeling

1. We note the container label and carton labeling includes the Medication Guide (MG) statement [redacted] (b) (4) However, the container/carton

[a] Topper, C. Label and Labeling Review for Elrexfio (BLA 761345). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 23. TTT ID No.: 2022-3129.

labeling does not include how the MG is provided (e.g., accompanied, enclosed, or provided separately) as required per 21 CFR 208.24(d). We recommend revising the statement to (b) (4) or something similar.

B. Container label

1. The manufacturer information [e.g., manufacturer name and logo] competes in prominence from critical product information (e.g., [proprietary name and established name]). Critical product information such as the proprietary name, nonproprietary name, and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15. We recommend relocating the manufacturer name and logo away from the proprietary name, for example, to the bottom of the label.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

CHRISTINA A TOPPER
06/16/2023 10:29:02 AM

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06/20/2023 03:58:49 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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***

Date of This Review:	May 23, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761345
Product Name, Dosage Form, and Strength:	Elrexfio (elranatamab-xxxx)[1] Injection, 76 mg/1.9 mL (40 mg/mL) and 44 mg/1.1 mL (40 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	December 19, 2022
TTT ID #:	2022-3129
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

[1] The nonproprietary name for BLA 761345 has not been determined yet. The nonproprietary name elranatamab-xxxx is used as a placeholder throughout this review.

1 REASON FOR REVIEW

As part of the approval process for 351(a) BLA 761345 Elrexfio (elranatamab-xxxx) Injection, we reviewed the proposed Elrexfio Prescribing Information (PI), Medication Guide, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Pfizer, Inc. submitted a 351(a) application to obtain marketing approval of Elrexfio (elranatamab-xxxx) Injection. Elrexfio is proposed for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

We performed a risk assessment of the proposed container labels, carton labeling, PI and Medication Guide for Elrexfio Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors.

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4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, PI, and Medication Guide that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Pfizer, Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights and Full Prescribing Information

1. Dosage and Administration

a. The route of administration is abbreviated as "SC". Presenting the route of administration as an abbreviation may lead to misinterpretation of the intended route of administration. We recommend revising "SC" to "subcutaneous(ly)".

2. As currently presented the table describing the dosage and dosing schedule lacks clarity. To prevent confusion, we recommend revising the table as follows:

ELREXFIO Recommended Dosing Schedule (2.1)			
Dosing Schedule	**Day**	**ELREXFIO Dose**	
Step-up Dosing Schedule	Day 1	Step-up dose 1	12 mg
	Day 4	Step-up dose 2	32 mg
	Day 8	First treatment dose	76 mg
Weekly Dosing Schedule	One week after first treatment dose and weekly thereafter (b) (4) (b) (4) **24**	Subsequent treatment doses	76 mg
Biweekly (Every 2 Weeks) Dosing Schedule ***Responders only week 25 onward**	(b) (4) and every 2 weeks thereafter	Subsequent treatment doses	76 mg

B. Highlights

1. Dosage and Administration

a. We recommend adding the statement, "See Full Prescribing Information for instructions on preparation and administration. (2.5)".

C. Full Prescribing Information

1. Dosage and Administration Section
   a. Section 2.1 Recommended Dosage
      i. We recommend deleting: (b) (4)

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[redacted] as this statement is not necessary and may be confused with section 2.3 regarding restarting Elrexfio after dosage delay.

2. Section 2.5 Preparation and Administration Instructions
    a. We recommend revising the Preparation section as follows:
        i. Remove the first statement “ELREXFIO vials [redacted] and do not contain any preservatives” as this information is stated in Section 16 already and is not needed here.
        ii. Revise Table 6 as follows for improved readability and organization

Table 6. Injection Volumes

Total Dose (mg)	Volume of Injection
12 mg	0.3 mL
32 mg	0.8 mL
76 mg	1.9 mL

        iii. We recommend including the following statements for clarity on preparation technique of the product:
Remove the appropriate strength ELREXFIO vial from refrigerated storage [2°C to 8°C (36°F to 46°F)].

Once removed from refrigerated storage, equilibrate ELREXFIO to ambient temperature [15°C to 30°C (59°Fto 86°F)] for at least XX minutes. Do not warm ELREXFIO in any other way.Withdraw the required injection volume of ELREXXFIO from the vial into an appropriately sized syringe.

        iv. We recommend revising and moving the following statements to its own section [redacted] and placed at the end of Section 2 “[redacted] If the prepared dosing syringe is not used immediately, store syringe between 2°C (36°F) to 30°C (86°F) for a maximum of 4 hours. [redacted] Revise to “If the prepared dosing syringe is not used immediately, store syringe between 2°C (36°F) to 30°C (86°F) for a maximum of 4 hours.".
    b. Administration of ELREXFIO
        i. We recommend removing the first statement [redacted] as it is not needed as

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this was already stated at the beginning of this section and does not need to be repeated.

ii. For improved clarity and readability, recommend revising the statement [redacted] to "Inject the required volume of ELREXFIO into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, ELREXFIO may be injected into the subcutaneous tissue at other sites (e.g., thigh).".

iii. Add the following statement: "Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact."

3. Section 3 Dosage Forms and Strengths
   a. As currently presented the dosage form is stated as [redacted] while the product is an injectable already in solution. We recommend revising the dosage form to "Injection".

4.2 RECOMMENDATIONS FOR PFIZER INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We recommend expanding the boxing currently around each strength to also include the concentration per mL (e.g. 40 mg/mL), so that the total quantity per total mL and the volume per mL is in the colored box and not overlooked.
2. We note that the dosage form and route of administration are presented on the same line below the nonproprietary name. We recommend separating this information by moving the route of administration below the dosage form for readability. In addition, we recommend bolding the route of administration to increase its prominence.
3. To ensure consistency with the prescribing information, we recommend revising the statement [redacted] to "Recommended Dosage: See Prescribing Information".
4. Revise the Statement of Dosage and Administration to both carton labeling and container labels to read [redacted] to be in alignment with PLR labeling format.

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B. Carton Labeling

1. The carton labeling does not contain instructions that this product must be administered by healthcare provider only. Failure to include instructions on the carton labeling may result in patients or caregivers administering the product, which may lead to medication errors. We recommend adding the statement [redacted] (b) (4) to the carton labeling. The statement will help alert patients, caregivers, and healthcare providers (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to their healthcare provider for administration. Alternatively, you can include it as part of the route of administration such that is states "For Subcutaneous Injection by a Healthcare Provider Only".
2. We recommend debolding the statement "No Preservative" as it appears more prominent than other information on the side panel.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Elrexfio received on December 19, 2022 from Pfizer Inc..

Table 2. Relevant Product Information for Elrexfio	
Initial Approval Date	N/A
Nonproprietary Name	elranatamab-xxxx
Indication	For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	76 mg/1.9 mL (40 mg/mL) and 44 mg/1.1 mL (40 mg/mL)
Dose and Frequency	(b) (4)
How Supplied	As a sterile, preservative-free, clear to slightly opalescent, and colorless to pale brown liquid solution supplied as follows: • One 76 mg/1.9 mL (40 mg/mL) single-dose vial in a carton. NDC: 0069-4494-02 • One 44 mg/1.1 mL (40 mg/mL) single-dose vial in a carton. NDC: 0069-2522-02
Storage	Store refrigerated at 2 °C to 8 °C (36 °F to 46 °F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.

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Container Closure	**Component**	**Description**
	Vial	5 mL (b) (4) clear glass vial.
	Vial Stopper	(b) (4)
	Seal	Flip-off design constructed of aluminum with a (b) (4) flip-off cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 28, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “Elrexfio” and “elranatamab” and “BLA 761345”. Our search identified no previous reviews.

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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,[a] along with postmarket medication error data, we reviewed the following Elrexfio labels and labeling submitted by Pfizer Inc..

- Container label received on 12/19/2022
- Carton labeling received on 12/19/2022
- Professional Sample Carton Labeling received on 12/19/2022
- Professional Sample Container Labeling received on 12/19/2022
- Prescribing Information (Image not shown) received on 12/19/2022, available from \\CDSESUB1\EVSPROD\bla761345\0002\m1\us\elranatamab-uspi-fpi-lab-1518-0-1-mg-1551-0-1-clean.pdf
- Medication Guide received on 12/19/2022, available from \\CDSESUB1\EVSPROD\bla761345\0002\m1\us\elranatamab-uspi-fpi-lab-1518-0-1-mg-1551-0-1-clean.pdf

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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05/24/2023 04:29:22 PM

CLINICAL INSPECTION SUMMARY

Date	5/24/2023
From	Leigh Marcus, M.D., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Natasha Kormanik, Regulatory Project Manager Rachel Ershler, M.D., Clinical Reviewer Bindu Kanapuru, M.D., Team Leader Nicole Gormley, M.D., Division Director Division of Hematologic Malignancies 2 (DHM2) Office of Oncologic Diseases (OOD)
BLA #	761345
Applicant	Pfizer, Inc.
Drug	Elranatamab
NME	Yes
Review Priority	Priority
Proposed Indication	For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody
Consultation Request Date	2/8/2023
Summary Goal Date	6/5/2023
Action Goal Date	8/4/2023
PDUFA Date	8/19/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study C1071003 were submitted to the Agency in support of this Biologic License Application (BLA) for elranatamab for the treatment of adult subjects with relapsed or refractory multiple myeloma who have received at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Two clinical investigators (CIs): Drs. Alexander Lesokhin (Site #1003) and Bertrand Arnulf (Site

#1102), as well as the sponsor, Pfizer, Inc., were inspected for Study C1071003.

Based on the inspection results of the above two CIs and the sponsor, no significant regulatory violations were identified. The clinical data generated by these CI sites are verifiable. The sponsor's oversight and monitoring of Study C1071003 were adequate. This study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Elranatamab administered by subcutaneous injection was being developed under IND 133940 for the treatment of adult subjects with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The sponsor has submitted the results of Study C1071003, an open-label, multi-center, nonrandomized, study to support efficacy and safety of elranatamab for the proposed indication.

Study C1071003

Study C1071003 was an open-label, multicenter, non-randomized, Phase 2 study to evaluate the efficacy and safety of elranatamab in RRMM participants who are refractory to at least one proteasome inhibitor (PI), one immunomodulatory drug (IMiD), and one anti-CD38 monoclonal antibody (mAb). Study C1071003 enrolled 2 independent and parallel cohorts:

- Cohort A: Subjects who have not received prior B-cell maturation antigen (BCMA)-directed therapy
  - 123 participants were enrolled and treated.

- Cohort B: Subjects who have received prior BCMA-directed antibody drug conjugate (ADC) or BCMA-directed CAR-T therapy, either approved or investigational.
  - 64 participants were enrolled and treated.

Eligible participants were required to have RRMM, refractory to at least one PI, one IMiD, and one anti-CD38 mAb, and their last anti-MM regimen, an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-2, and all subjects were required to have measurable disease.

The study was comprised of 3 periods: a screening and enrollment period, a study intervention period, and a post study follow up period. The proposed dosing regimen included step-up doses of elranatamab 12 mg subcutaneously (SC) on Day 1 and 32 mg SC on Day 4, followed by a full treatment dose of 76 mg weekly, from Week 2 to Week 24.

Treatment continued until disease progression, unacceptable toxicity, or withdrawal of

consent. For subjects who have received at least 24 weeks of treatment and have achieved a partial response or better, the dose interval transitioned from weekly to an every two-week schedule.

The primary endpoint for each independent cohort was to determine the objective response rate (ORR) of elranatamab as assessed by blinded independent central review (BICR), as defined by International Myeloma Working Group (IMWG).

The trial was conducted in 53 sites in 10 countries. Subjects first enrolled to Study C1071003 on February 2, 2021. Data cut-off date for the primary analysis was October 14, 2022. The study was ongoing during the time of the inspections.

Rationale for Site Selection

Two CIs: Drs. Lesokhin (Site #1003) and Arnulf (Site #1102), as well as the sponsor, Pfizer, Inc., were requested for clinical inspections in support of the application. The clinical sites were chosen primarily based on insufficient domestic clinical site data thus inspection of a foreign clinical investigator, risk ranking in the BIMO clinical investigator site selection tool (CISST), numbers of enrolled subjects, and prior inspectional history, each of which may have an impact in the review division's clinical decision-making process.

Inspection Focus

The inspections were focused on subjects with RRMM treated with elranatamab and had not received prior BCMA-directed therapy enrolled on Cohort A, in which the Sponsor seeks an indication.

III. RESULTS

1. Alexander Lesokhin, M.D./Site: #1003
   1275 York Avenue
   New York, NY 10065

   Inspection Dates: 4/6/2023 – 4/12/2023

   This was a comprehensive, PDUFA routine inspection of Dr. Lesokhin. This was his first FDA inspection.

   At this site for Study C1071003, 16 subjects were screened and 14 subjects were enrolled, of which 9 subjects were enrolled on Cohort A. Of the 9 subjects in Cohort A, at the time of the inspection, 2 subjects remained on treatment, 4 subjects discontinued due to disease progression or death, and 3 subjects withdrew: 1 due to hospitalization, 1 due to "patient's request", and one unspecified and died later.

During the inspection, subject records reviewed included informed consent documents (ICD), subject eligibility, concomitant medications, primary efficacy endpoint data, adverse events/serious adverse events, and protocol deviations. The regulatory records reviewed included IRB submissions for initial approval and continuing reviews; protocol amendments; Form 1572s, financial disclosures, test article accountability, training records, and Curriculum Vitae (CVs) for the Principal Investigator (PI) and study team members.

All of the 9 subjects' ICDs in Cohort A were well-documented in each subject's file. The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

Three protocol deviations were discussed as noted below:

1. Investigational Product (IP) was administered without following dosage modification for hematologic and non-hematologic toxicity as defined in the protocol for Subjects # (b) (6) (b) (6)
2. Subject # (b) (6) did not meet inclusion criteria 6 (Refractory to proteasome inhibitor).
3. Subject # (b) (6) experienced a serious adverse event (SAE) of hospitalization for Covid-19 pneumonia, which was not reported to the Sponsor until 9 days after the event, outside of the specified timeframe in the protocol.

Reviewer's comment: The administration of elranatamab without dose modification was reported as major protocol deviations in the clinical study report in the BLA submission. For Subject # (b) (6), on (b) (6) the dose modification did not occur, and on (b) (6), the subject experienced a SAE of upper GI hemorrhage that required hospitalization in which drug was interrupted; the SAE resolved on (b) (6). It is unclear if the unmodified elranatamab dose may have contributed the upper GI hemorrhage and hospitalization in Subject # (b) (6) however, bleeding is not a potential known side effect of elranatamab and the CI assigned "not related" as not causality to the drug. For the other 2 subjects in which the dose modification did not occur, there were no AE/SAE subsequently reported. Subject # (b) (6) did not meet inclusion criteria and this protocol deviation was reported in clinical study report; it is an isolated event and unlikely to have a significant impact on overall efficacy. The late reporting of the unrelated SAE (Covid-19 pneumonia) would not change the safety profile of elranatamab.

In general, the inspection verified adequate source data for the inspected study subjects.

2. Bertrand Arnulf, M.D./Site #1102
   1 Avenue Claude Vellefaux
   Paris, 75010
   France

   Inspection Dates: 4/3/2023 – 4/7/2023

This was a comprehensive, PDUFA routine inspection of Dr. Arnulf. This was his first FDA inspection.

At this site for Study C1071003, 15 subjects were enrolled, of which 11 subjects were enrolled on Cohort A. All 11 subjects were found to discontinue treatment: 3 subjects due to an adverse event ([AE]: Subject # (b) (6) due to serious (SAE) Guillain Barre Syndrome, Subject # (b) (6) due to sarcopenia, and Subject # (b) (6) due to sepsis), 4 subjects due to progressive disease (PD), and 4 subjects due to death. At the time of this inspection 2 subjects were still on study.

During the inspection, subject records for 11 subjects enrolled on Cohort A were reviewed including informed consent documents (ICD), eligibility, SAEs, efficacy endpoint data and treatment response, spot checks for concomitant medications, and study visit assessments. The regulatory records reviewed included IRB submissions for initial approval and continuing reviews, independent ethics committee approvals, protocol amendments, financial disclosures, test article accountability, training records, and Curriculum Vitae (CVs) for the Principal Investigator (PI) and study team members.

All of the 11 subjects ICDs was well-documented in each subject's file. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint data were verifiable except few discrepancies as described below.

There were inconsistencies with documentation including endpoint data discrepancies noted. For Subjects # (b) (6) the site entered a response into the EDC; subsequently, there were queries which appeared to be from the independent review committee (IRC) asking to change their entry, which the site coordinator did without discussing with the CI. The CI did not agree with the queries and stood by the initial assessment. The site coordinator was reminded that anything that is not a data entry error needs to be discussed with the investigators.

Reviewer's comment: Changing endpoint data at the site did not impact the efficacy outcome as the IRC was responsible for assessment of the primary efficacy endpoint.

In general, the inspection verified adequate source data for the inspected study subjects.

3. Pfizer, Inc.
   445 Eastern Point Road
   Groton, CT 06340

   Inspection Dates: 4/11/2023 – 4/19/2023

   This inspection covered sponsor's study conduct related to Study C1071003, concentrating on review of the subjects with RRMM enrolled on Cohort A, for efficacy and safety. The review focused on the clinical investigator sites chosen for inspection, Sites #1003 and #1102,

however, 8 sites monitoring files were reviewed during the inspection.

The most recent inspection of Pfizer was on 10/12-28/2022 and did not have any clinically significant regulatory issues.

Records reviewed during the inspection included:

- Selection of clinical investigators, sites, and monitors
- Form FDA 1572s and CVs
- Personnel training documents
- Contract and agreements:
  - [redacted] (b) (4) provided the contract research organization [CRO] project management and investigator site monitoring
  - [redacted] (b) (4) provided the independent assessment of imaging studies)
- Study monitoring plans and data review committee activities
- Data collection and handling
- Safety reporting and handling
- Study documents
- Standard operating procedures (SOP)
- Investigational product disposition
- Financial disclosures

Eight sites (Sites # 1003, 1102, 1007, 1019, 1046, 1068, 1074, and 1109) monitoring files were reviewed during the inspection; the review focused on the clinical investigator site chosen for inspection, Site # 1003 and 1102.

Appropriate steps were taken by the sponsor to bring noncompliant sites into compliance. No sites were found to have inadequate monitoring. There was no under-reporting of AE/SAEs.

Overall, the sponsor's oversight and monitoring for Study C1071003 appear adequate.

{See appended electronic signature page}

Leigh Marcus, M.D. Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D. Team Leader

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cc:

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JENN W SELLERS
05/24/2023 11:42:51 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 22, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Natasha Kormanik
DHM2

Subject: QT Consult to BLA761345 (SDN 0002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/26/2023 regarding the sponsor's evaluation of QT effects for elranatamab. We reviewed the following materials:

- Sponsor's elranatamab QT evaluation report (BLA761345 / SDN 2);
- Sponsor's Proposed Labeling (BLA761345 / SDN 2);
- Sponsor's summary of clinical pharmacology studies (BLA761345 / SDN 2);
- Sponsor's clinical overview (BLA761345 / SDN 2);
- Sponsor's integrated summary of safety (BLA761345 / SDN 2);
- Investigator's Brochure (IND133940/SDN 286);
- Highlights of clinical pharmacology and cardiac safety (BLA761345 / SDN 10).

1 Responses for the Sponsor

IRT's response: Please convey the following to the sponsor.

Overall, the sponsor's findings are consistent with the fact that large, targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and therefore are not expected to cause concentration dependent prolongation of the QTc interval (ICH E14 Q&A 6.3).

2 Internal Comments for the Division

- *None*

3 BACKGROUND

3.1 Product Information

Elranatamab (PF-06863135) is a T-cell redirecting bispecific IgG2 antibody (BsAB) targeting both B-cell Maturation Antigen (BCMA) and the T-cell co-receptor cluster of differentiation 3 (CD3). Elranatamab is derived from anti-BCMA and anti-CD3 with the resulting 4-chain bispecific antibody covalently linked via 5 inter-chain disulfide bonds.

The sponsor (Pfizer Inc.) is developing elranatamab (ELREXFIO™) for treatment of adult patients with relapsed/refractory multiple myeloma (RRMM) who have received at least (b) (4) classes of prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The recommended doses of ELREXFIO subcutaneous (SC) injection are step-up doses of 12 mg on Day 1 and 32 mg on Day 4 followed by a full treatment dose of 76 mg Q1W, from week 2 to week 24. For patients who have received at least 24 weeks of treatment with ELREXFIO and have achieved a response, the dose interval should transition to Q2W schedule. Treatment with ELREXFIO should continue until disease progression or unacceptable toxicity.

The clinical pharmacology of elranatamab is presented in the summary of clinical pharmacology studies. In brief, elranatamab is estimated to have median (95% prediction interval) half-life of 25 (9.6 - 70) days. Maximum elranatamab exposure is expected on week 24 as the dosing intensity is reduced to Q2W for responding patients thereafter. The median accumulation ratio after 24 weeks of 76 mg QW dosing for free and total elranatamab Cmax was estimated to be 6.6 and 4.8, respectively. According to the sponsor's PK analysis, the PK of free and total elranatamab is not affected by race, anti-drug antibody, renal function, age, sex, body weight, and mild hepatic impairment. The PK of free elranatamab is impacted by baseline levels of sBCMA. A trend for lower free elranatamab exposure was observed with increased baseline sBCMA. The impact of moderate and severe hepatic impairment or ESRD on PK of elranatamab has not been characterized.

3.2 Sponsor's position related to the question

The sponsor has conducted concentration-QT analysis of sparse, time matched PK/ECG data pooled from 2 phase 1 studies (C1071001, and C1071002), 1 phase 1 /2 study (C1071009), and 1 phase 2 study (C1071003). Details of dose and PK/ECG data collection schedule are presented in the sponsor's QT evaluation report. In brief, doses ranging from 0.1 µg/kg to 76 mg were tested intravenously or subcutaneously in multiple ascending (C1071001), dose expansion (C1071002), dose step-up priming and maintenance (C1071009), and the phase 2 registration study (C1071003). Single and triplicate ECGs were both preformed in the studies. Each study had its own PK and ECGs collections schedule, but mostly pre-dose on days 1, 8, 15, and 22. Additional PK/ECGs were collected on days 2 (24 hours), 4 (72 hours) post day 1 dose.
The results from the sponsor's concentration-QT analysis indicate that neither free nor total elranatamab was associated with concentration-dependent QTc interval prolongation.
In this analysis, neither total nor free elranatamab concentration was found to affect RR intervals. Correction of the QT interval data for the dependence on the RR interval (heart rate) was pre-

specified to be Fridericia's correction factor and it was confirmed to be a sufficient correction method.

The population estimate for the slope describing the QTcF-total elranatamab concentration relationship was -0.0000673 msec/(ng/mL) and the 95% CI for the slope based on bootstrap was -0.000145 msec/(ng/mL) to -0.00000738 msec/(ng/mL). Similarity, the population estimate for the slope describing the QTcF-free elranatamab concentration relationship was -0.0000387 msec/(ng/mL) and the 95% CI for the slope based on bootstrap was -0.000139 msec/(ng/mL) to 0.0000329 msec/(ng/mL).

The expected median change in QTcF from baseline for total elranatamab was -1.572 msec (95% CI: -3.303 to -0.178) at an average observed plasma maximum concentration (Cmax) of 22760.5 ng/mL. For free elranatamab, the expected median change in QTcF from baseline was -0.583 msec (95% CI: -1.929 to 0.454) at an average observed plasma Cmax of 13941.9 ng/mL.

CONCLUSION(S)

Based on the results of the analysis performed in this report:

- lranatmab concentrations (either free or total) did not affect heart rate.
- QTcF intervals have a negative correlation with elranatamab serum concentrations (both total and free).
- The upper bound of 95% CI for both of the models predicted changes in QTcF at the mean observed plasma Cmax for therapeutic concentrations were less than 5 milliseconds, suggesting the effect of total or free elranatamab exposure on QTc prolongation is very minimal.
- The population covariates (e.g. age, race and gender) tested did not have a statistically significant impact on the change in QTc interval.

Reviewer's comments: *The reviewer's findings are consistent with the fact that large, targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and therefore are not expected to cause concentration dependent prolongation of QT interval.*
In general we do not recommend concentration-QTc analysis for large molecules which are unlikely to interact/block with hERG ion channels.

3.3 Nonclinical Cardiac Safety

Independent safety pharmacology studies were not conducted with elranatamab. However, no treatment-related effects were observed for cardiovascular endpoints (ie, electrocardiogram) and no study observations indicated any adverse elranatamab-related changes in respiratory or CNS function in the 3-month pivotal toxicology study in monkeys.

3.4 Clinical Cardiac Safety

According to the sponsor's clinical overview, sinus tachycardia and tachycardia were reported in 6.4% and 4.9% of participants, respectively. Bradycardia was reported in 1.1% of participants. Hypertension and Hypotension were reported in 7.2% and 8.3% of participants, respectively. There were no clinically meaningful changes in QTcF in participants treated with elranatamab. Categorization of ECG data for the safety pools by maximum on-treatment QTcF measurement and maximum increase of QTcF from baselines is provided in Module 5.3.5.3 Safety Appendix

Table 14.3.6.2.1 and shift summary results of ECGs on-treatment are provided in Module 5.3.5.3 Safety Appendix Table 14.3.6.2.2. In the overall safety population (Pool 3):

- The majority of participants had a maximum on-treatment QTcF of <450 msec (76.4%) or ≥450 to ≤480 msec (18.5%).
- A total of 8 participants (3.1%) had a maximum on-treatment QTcF of >500 msec. However, of these, 2 participants had a QTcF >500 msec at baseline and 1 participant had a QTcF of >480-500 msec at baseline and 4 participants had Electrocardiogram QT prolonged listed as an ongoing event in their medical history (Module 5.3.5.3 Safety Appendix Table 14.1.3.3; 14.3.6.2.2).
- A total of 10 participants (3.9%) had a QTcF interval change from baseline of >60 msec.
- A total of 4 participants (1.5%) had all-causality AEs of Electrocardiogram QT prolonged (2 Grade 1 and 2 Grade 3) (Module 5.3.5.3 Safety Appendix Table 14.3.1.2.2). One (0.4%) AE of Electrocardiogram QT prolonged (Grade 1) was considered treatment related (Module 5.3.5.3 Safety Appendix Table 14.3.1.3.2).

3.5 Summary results of prior QTc assessments

See section 3.2

3.6 Relevant details of planned Phase 3 study

NA

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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