

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761151Orig1s000

**RISK ASSESSMENT AND RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761151
PDUFA Goal Date	May 21, 2023
Nexus TTT #	2022-2955
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	October 16, 2023
Subject	Evaluation of Need for a REMS
Established Name	Bimekizumab
Trade Name	Bimzelx
Name of Applicant	UCB, Inc.
Therapeutic Class	Humanized interleukin-17A and F antagonist
Formulation(s)	160 mg/mL in single-dose prefilled syringe and single-dose autoinjector for injection
Dosing Regimen	320 mg subcutaneously injected at weeks 0, 4, 8, 12, and 16, thereafter every 8 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) serves as an update to the October 8, 2021 REMS determination review¹ to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Bimzelx (bimekizumab) is necessary to ensure the benefits outweigh its risks.

UCB, Inc resubmitted biologics license application (BLA) 761151 on November 21, 2022 in response to a Complete Response Letter due to deficiencies related to facilities inspections. The resubmission contained new clinical data, including additional safety data from the open-label extension trial (PS0014) and data from a Phase3b, multicenter, randomized, double-blind, active-comparator controlled trial (PS0015).

The review team identified a new safety signal of a possible increased risk of suicidal ideation and behavior (SI/B) associated with the use of bimekizumab based on the new safety data which included one report of a completed suicide and three suicide attempts, and a re-analysis of pooled data from the controlled trials which showed a numerical imbalance in positive responses on the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) in the bimekizumab group compared to the control group. Given the serious potential risk of SI/B, the Division of Dermatology and Dentistry (DDD), the Division of Psychiatry (DP), and DRM evaluated the appropriate risk mitigation measures and discussed the strength of the signal and risk mitigation options with CDER leadership.

There is a possible increase in the risk of SI/B with bimekizumab use based on the available data. Higher rates of SI/B and depression have been observed in patients with psoriasis compared to the general population; however, background rates vary across studies. The rate of SI/B in the bimekizumab clinical development program may surpass the background rate depending on which studies are used for comparison. There were no identifiable risk factors and events occurred in patients both with and without psychiatric histories. The pivotal studies were not powered to observe differences in rates of SI/B between the bimekizumab-treated group and placebo or the active controls. Additionally, the clinical development program employed risk mitigation measures such as excluding patients with history or risk factors for SI/B, prospective monitoring, and discontinuation criteria; therefore, the risk of SI/B in the general psoriasis population may not be fully characterized. Although bimekizumab is approved in several other jurisdictions, the Agency is not aware of any post-marketing signal for this risk to date. The review team completed additional statistical analyses on the SI/B data; however, conclusions were limited due to the small number of events and wide confidence intervals.

DDD concluded that the possible increased risk of SI/B associated with the use of bimekizumab will be communicated to prescribers through a Section 5 – Warning and Precaution, along with additional information in Section 6 and Section 17 of the prescribing information and communicated to patients through the Medication Guide.

Based on the review team's analysis of the available data, DRM has determined a REMS is not necessary to ensure the benefits of bimekizumab outweigh its risks. Labeling, including a Medication Guide, will be used to convey the possible increased risk of SI/B associated with bimekizumab use to prescribers and

patients. If new safety information becomes available, DRM can re-evaluate the need for additional risk mitigation strategies.

1. Introduction

This review by the Division of Risk Management (DRM) serves as an update to the October 8, 2021 REMS determination review¹ to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Bimzelx (bimekizumab) is necessary to ensure the benefits outweigh its risks.

UCB, Inc (hereafter referred to as the Applicant) originally submitted a Biologics Licensing Application (BLA) 761151 on July 15, 2020 for bimekizumab with the proposed indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.²

DRM completed a REMS Determination review on October 8, 2021 and concluded that based on the information available, a REMS was not necessary as the benefit-risk profile was acceptable and risk mitigation beyond labeling was not required.¹ At that time, draft labeling did not include the risk of suicidal ideation and behavior (SI/B) or any specific psychiatric warnings.^{3,4} A Complete Response (CR) letter was issued to the Applicant on May 12, 2022 due to deficiencies related to facilities inspections.⁵

The Applicant resubmitted BLA 761151 as a Class 2 resubmission on November 21, 2022.⁶ The resubmission contained new clinical data, including additional safety data from the open-label extension trial (PS0014) and data from a Phase 3b, multicenter, randomized, double-blind, active-comparator controlled trial (PS0015). The new clinical data included a report of a completed suicide and three suicide attempts. In response, the Division of Psychiatry (DP) was consulted to review the new clinical data and also completed a re-analysis of the pooled data from the controlled studies related to this risk. The review team identified a new safety signal of a possible increased risk of SI/B associated with the use of bimekizumab which is the focus of this review.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for BLA 761151 relevant to this review cycle:

- **11/21/2022:** Applicant resubmitted BLA 761151 in response to the CR Letter for facilities inspection deficiencies issued on May 12, 2022. The resubmission contained new clinical data.
- **05/03/2023:** A teleconference meeting was held to inform the Applicant that the Agency identified a new potential safety signal of SI/B associated with the use of bimekizumab.

- **05/04/2023:** The Agency issued a General Advice Letter that included a summary of the May 3, 2023 teleconference.
- **05/10/2023:** A teleconference was held between the Agency and Applicant. The Applicant did not agree with a SI/B safety signal and provided their rationale.
- **05/12/2023:** The Applicant submitted updated labeling to incorporate language to address the Agency's concerns about a safety signal for SI/B. The Applicant proposed changes to Section 6 – Adverse Events, Section 17 – Patient Counseling, and the Medication Guide.
- **06/05/2023:** The Division of Psychiatry (DP) completed a new consult which included review of the new safety data and a re-analysis of the data in the controlled trials.
- **06/21/2023:** Teleconference with Applicant regarding risk management strategies for SI/B. The Agency discussed proposed labeling and additional risk management measures including a REMS.
- **06/28/2023:** The Agency issued a General Advice Letter which included a summary of the June 21, 2023 teleconference and Agency responses to the Applicant's comments and questions related to the safety signal.
- **07/10/2023:** The Applicant submitted updated labeling to include the risk of SI/B as a Section 5 – Warning and Precaution. (b) (4)
- **09/29/2023:** The Applicant submitted updated labeling incorporating Agency feedback on communicating the risk of SI/B.

3. Risk Assessment & Safe-Use Conditions

The Applicant's resubmission included additional safety data from an open-label extension trial (PS0014) in 1343 subjects and an additional, ongoing Phase 3b multicenter, randomized, double-blind active-comparator-controlled, parallel group trial (PS0015) in 691 subjects. DP was consulted to review the new psychiatric safety information (refer to the DP consult review⁷ completed on June 5, 2023 for their complete assessment). The new safety data included a report of a completed suicide and three cases of attempted suicide associated with bimekizumab. Based on this new safety signal, DP re-analyzed all data related to the risk of SI/B.

3.1. Suicidal ideation and behavior

Suicidal ideation and behavior (SI/B) was an adverse event of interest in the psoriasis clinical development program for bimekizumab because Siliq (brodalumab), an interleukin-17 receptor antagonist, is approved with a REMS to mitigate the risk of suicidal ideation and behavior and studies suggest that the risk of SI/B may be higher in patients with psoriasis than the general population.⁸⁻¹¹ The bimekizumab clinical trials excluded patients with a history of suicide attempt in the past 5 years, recent

SI/B, moderately severe or severe major depression. In addition, protocols included prospective patient monitoring for depression using the Patient Health Questionnaire-9 (PHQ-9)^a and for SI/B using the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)^b and pre-specified discontinuation criteria for neuropsychiatric events.¹²

There were no completed suicides or suicide attempts reported in the original submission, and the first DP consult did not recommend specific psychiatric warning language for bimekizumab based on the data that was available during the last review cycle. During the resubmission, the Applicant submitted new safety information which included one report^c of a completed suicide and cases of serious neuropsychiatric events, including suicide attempts.

A completed suicide was reported for a 39 year-old white male with no prior psychiatric history 718 days after starting bimekizumab during the open-label trial. Notably, the patient had achieved complete skin clearance and previous PHQ-9 and eC-SSRS scores were negative. The subject was reported to have unspecified “financial issues; however, no additional details were available to assess whether these were contributing factors. Although the timing of the suicide was nearly 2 years after treatment initiation, the DP consultant noted that the pharmacodynamics of suicide risk are not clear and that the drug may “alter the brain such that the patient may be more likely to suicide when presented with external stressors”.⁷ The DP consultant concluded that suicide is a rare event; therefore, a case in a subject without previous psychiatric history is a potential signal and should be considered possibly drug-related.⁷

There were 14 cases of serious neuropsychiatric AEs in subjects exposed to bimekizumab in PS0014 and PS0015. The DP consultant concluded that these cases did not demonstrate a clear signal of SI/B risk associated with bimekizumab as most were complicated by a past psychiatric history and/or situational stressors. However, when coupled with the completed suicide case the DP consultant concluded these could be viewed as consistent with a possible drug-related risk.⁷

^a The Patient Health Questionnaire (PHQ-9) is a 9-item multipurpose instrument for measuring the severity of depression. Scores range from 0 to 27 with higher scores indicating a worse state. A score of 5 to 9 indicates minimal symptoms of depression. A score of 10 to 14 indicates minor depression, dysthymia, or mild major depression. A score of 15 to 19 indicates moderately severe major depression and a score ≥ 20 indicates severe major depression.

^b The Columbia-Suicide Severity Rating Scale is an assessment tool that evaluates suicidal ideation and behavior. It is a prospective tool with probing questions to inquire about the risk of suicidal ideation and behavior. It defines 11 categories including five subtypes of suicidal ideation (passive wish to be dead to active suicidal ideation with a plan and intent), five subtypes of suicidal behavior (preparatory acts to completed suicide), and self-injurious behavior without suicidal intent. Additional information available: <https://cssrs.columbia.edu/>.

^c The Applicant reports this suicide is “unconfirmed” as there was no objective confirmation of the death despite repeated efforts to obtain more information.

The DP consultant re-evaluated data on SI/B from Studies PS0008, PS0009, and PS0013 using a pool of subjects from the initial treatment period of the placebo/active controlled phase.

There was a numeric imbalance in positive eC-SSRS responses during the phase 3 trials with 17 positive responses in bimekizumab-treated patients (1.7%) compared to 1 in placebo-treated patients (0.6%). The majority of positive responses were for suicidal ideation, category 1, which reflects a passive wish to be dead without active suicidal ideation. The DP consultant also compared bimekizumab to active controls (adalimumab and ustekinumab) from Studies PS0008 and PS0009 and concluded the comparison appeared mixed. In study PS0008, 8 bimekizumab-treated patients reported positive responses to the eC-SSRS (2.6%) compared to 3 adalimumab-treated patients (1.9%). In study PS0009, 3 bimekizumab-treated patients (0.9%) and 3 ustekinumab (1.8%) reported positive responses to the eC-SSRS.

In addition to the clinical development program for psoriasis, the team also looked at the clinical development program for other indications. No completed suicides have been reported in the other bimekizumab clinical development programs for other indications; however, there were cases of suicide attempts and suicidal ideation. For hidradenitis suppurativa, the Applicant reports there were two suicide attempts with an exposure-adjusted incidence rate of 1.5/1000 PY. For axial spondyloarthritis and ankylosing spondylitis, there was a suicide attempt and one case of suicidal ideation. There was a suicide attempt in the psoriatic arthritis development program. The majority of these subjects had a history of a psychiatric disorder.¹³

Bimekizumab is approved in 39 countries worldwide without labeling related to SI/B or neuropsychiatric events.^{6,13,14} The Applicant reports that there is no signal for completed suicides or suicide attempts in the postmarketing data from other countries where bimekizumab is marketed (exposure >8850 patient years). However, the DP consultant notes that these events are underreported and the absence of cases provides limited support for safety given suicides are rare event.⁷

The DP consultant concluded that the available data are consistent with a possible signal for an association between SI/B and bimekizumab. DP recommended that labeling reflect a potential association with SI/B through a Boxed Warning, a Section 5-Warning and Precaution, and described in Section 6. The DP reviewer did not recommend a REMS.⁷

Additional statistical analyses were performed to further characterize the signal for SI/B associated with bimekizumab use.¹³ The additional analysis of eC-SSRS data from two placebo-controlled trials (PS0009 and PS0013) estimated a Mantel-Haenszel risk difference for the proportion of subjects who experienced new onset SI/B in these two trials over 16 weeks of 1.19% (-0.34%, 2.72%) and the corresponding Relative Risk of 3 (0.39, 22.74). This analysis shows a numerical imbalance suggesting possible increased risk of SI/B associated with bimekizumab relative to placebo over 16 weeks. For the active-controlled trials (PS0008, PS0009, and PS0015), the Mantel-Haenszel risk difference for the proportion of subjects who experienced SI/B in these three trials over 16 weeks was -0.29% (-1.41%, 0.84%) and the corresponding Relative Risk was 0.80 (0.34, 1.85). Conclusions based on these additional analyses are limited due to the small number of events and wide confidence intervals.

DDD concluded that based on the available data, given uncertainties in the strength of the signal, the potential risk of SI/B will be communicated in Section 5 of labeling as a Warning and Precaution.¹³ See Section 6 for additional discussion on risk management activities.

4. Expected Postmarket Use

Bimekizumab is likely to be prescribed by dermatologists and is expected to primarily be used by patients in the outpatient setting. Although many of the risks associated with bimekizumab are similar to other biologics approved for psoriasis, bimekizumab will have a warning and precaution for the risk of SI/B and a Medication Guide to convey important risk messaging to prescribers and patients.

5. Risk Management Activities Proposed by the Applicant

5.1. Other Proposed Risk Management Activities

The Applicant did not submit a REMS with the original application but submitted a risk management plan.^d No additional risk management activities were included in the resubmission. However, as a result of the discussions regarding the new safety signal of a possible increased risk of SI/B associated with bimekizumab, the Applicant proposed additional measures to address the Agency's concerns.

The Applicant proposed the following risk management activities:

- Enhanced pharmacovigilance for SI/B cases
- Patient Support Program a voluntary program which proposes education via proactive outreach by nurses
- Distribution via specialty pharmacy network with additional measures for adverse event reporting

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and we recommend that the Division of Pharmacovigilance be consulted for review of the enhanced pharmacovigilance plan. We note that last two bullets are proposed voluntary activities and we do not object to them.*

^d The risk management plan submitted with the original application proposed additional pharmacovigilance activities including plans to conduct a real-world outcomes study to further monitor the risks associated with bimekizumab, to establish a pregnancy registry, and to conduct a retrospective cohort study to evaluate exposure of bimekizumab in pregnancy.

6. Discussion of Need for a REMS

The benefit of bimekizumab for the treatment of moderate to severe plaque psoriasis was demonstrated in two pivotal phase 3 placebo-controlled trials, PS0009 and PS00013.^{3,15}

The review team identified a new safety signal of a possible increased risk of SI/B associated with the use of bimekizumab based on the new safety data which included one report of a completed suicide and three suicide attempts, and a re-analysis of pooled data from the controlled trials which showed a numerical imbalance in positive responses on the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) in the bimekizumab group compared to the control group. Given the seriousness of the potential risk, DDD, DP, and DRM evaluated appropriate risk mitigation measures, including a boxed warning and whether a REMS was necessary to ensure the benefits of bimekizumab outweigh the risk of SI/B. The strength of the signal and appropriate risk mitigation measures was discussed with both the REMS Oversight Committee and the Medical Policy and Program Review Council (MPPRC).

Suicidal ideation and behavior is a serious, but rare event. Higher rates of SI/B and depression have been observed in patients with psoriasis compared to the general population, although background rates are variable in the literature due to differences in methodology and disease severity.^{10,11,13} The clinical review team concluded the rate of SI/B in the clinical development program for bimekizumab may or may not surpass the background rate depending on which studies are used for comparison.¹³

The timing of SI/B was unpredictable in the bimekizumab clinical trials and events occurred throughout treatment including during maintenance. There were no identifiable risk factors and events occurred in patients both with and without psychiatric histories. The trials were not powered or designed to observe differences in rates of SI/B between bimekizumab groups and placebo or the active control groups. The clinical development program employed risk mitigation measures such as excluding patients with history or risk factors for SI/B, prospective monitoring, and discontinuation criteria; therefore, the risk of SI/B in the general psoriasis population may not be fully characterized. The additional analyses of the eC-SSRS data performed by the review team were limited by the small number of events and wide confidence intervals making conclusions challenging.

Bimekizumab is approved in 39 countries worldwide without labeling related to SI/B or neuropsychiatric events.^{6,13,14} The Agency is not aware of data suggesting a signal for completed suicides or suicide attempts in foreign postmarketing data. A biologic mechanism for bimekizumab and the risk of SI/B has not been established. The role of cytokines, including IL-17, in suicidality has been explored but is not well understood.^{16,17} High levels of IL-17 have been linked to neuroinflammation and depression; however, the role IL-17 or products that impact IL-17 play in SI/B is not clear and likely complex.¹⁶

During the risk assessment, the review team reviewed the rates of suicide and suicide attempts for other biologics approved for psoriasis. However, comparison of this data is limited as there were significant differences in patient populations, patient monitoring, and discontinuation criteria.

The anticipated prescribing population is dermatologists. In 2019, the American Academy of Dermatology and National Psoriasis Foundation published joint guidelines of care for the management

and treatment of psoriasis with awareness and attention to comorbidities which includes recommendations regarding the need to screen and monitor for mental health conditions (such as SI/B) in patients with psoriasis. Incorporating these recommendations into national guidelines may be increasing prescriber awareness regarding the risk of SI/B in this population.¹⁸ Additionally, another product, Siliq (brodalumab) was approved with a REMS to mitigate this risk. Some evidence suggests dermatologists understand and are knowledgeable about the risk of SI/B and need for monitoring.¹⁹ Despite knowledge of the risk, routine screening for depression and SI/B may not be fully incorporated into clinical practice.¹⁹ SI/B is not predictable and may occur at any point during therapy; therefore, patient awareness of the risk and how to seek help and medical attention is important. These care gaps were considered during risk management discussions. If approved, labeling (including a Medication Guide) will convey important information about the risk of SI/B for prescribers and patients. The need for patients, as well as caregivers and family, to monitor for emergence of worsening of depression, mood changes, and SI/B and the need for patients to seek medical attention or call the National Suicide Crisis line at 988 is included in labeling and the Medication Guide.

After considering DP's review and feedback from the MPPRC, DDD determined the risk of SI/B associated with the use of bimekizumab will be communicated in Section 5 (Warning and Precaution), Section 6 (Adverse Reactions), Section 17 (Patient Counseling) and a Medication Guide. DRM is in alignment with this decision based on the review team's analysis of the available data.

While the risk of SI/B is serious, based on the data available, DRM is not recommending a REMS for bimekizumab. Labeling, including a Medication Guide, will be used to convey the possible increased risk of SI/B to prescribers and patients. If new safety information becomes available, DRM can re-evaluate the need for additional risk mitigation strategies.

7. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of bimekizumab outweigh the risks. The possible increased risk of SI/B associated with bimekizumab will be communicated to patients and prescribers through labeling, including a Medication Guide.

At the time of this review, labeling negotiations were ongoing. Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

8. Appendices

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
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Application Type	BLA
Application Number	761151
PDUFA Goal Date	October 15, 2021
OSE RCM #	2020-1497
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
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Subject	Evaluation of Need for a REMS
Established Name	Bimekizumab
Trade Name	Bimzelx
Name of Applicant	UCB, Inc.
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Formulation(s)	160 mg/mL in single-dose prefilled syringe and single-dose autoinjector for injection
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Bimzelx (bimekizumab) is necessary to ensure the benefits outweigh its risks. UCB, Inc submitted a Biologics Licensing Application (BLA) 761151 for bimekizumab with the proposed indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The risks associated with bimekizumab include the risk of infections, liver biochemical abnormalities, and inflammatory bowel disease. The Applicant did not submit a REMS with this application but submitted a risk management plan. The risk management plan proposed additional pharmacovigilance activities including plans to conduct a real-world outcomes study to further monitor the risks associated with bimekizumab, to establish a pregnancy registry, and to conduct a retrospective cohort study to evaluate exposure of bimekizumab in pregnancy.

DRM has determined that a REMS is not needed to ensure the benefits of bimekizumab outweigh its risks. The benefit for the treatment of moderate to severe plaque psoriasis was demonstrated as bimekizumab resulted in a statistically significant difference compared to placebo in the co-primary endpoints in the pivotal, placebo-controlled phase 3 trials. The risks associated with bimekizumab are similar to other approved IL-17 inhibitors used for the treatment of psoriasis with the notable exception of the possible risk of drug-induced liver injury. In clinical trials, there were imbalances in liver enzyme elevations (liver biochemical abnormalities) in the bimekizumab group compared to placebo. However, there were no definite or probable Hy's Law cases, liver transplants, or deaths. Drug-induced liver injury has not been reported with other IL-17 inhibitors; however, it has been associated with other agents used for the treatment of psoriasis. Labeling will be used to communicate the risk of infections, inflammatory bowel disease, and liver enzyme abnormalities in warnings and precautions including the need to monitor liver enzymes, alkaline phosphatase, and bilirubin prior to initiation and periodically throughout therapy with bimekizumab. The label will include a limitation of use statement to avoid bimekizumab therapy in patients at increased risk of severe hepatic injury. The other risks associated with bimekizumab are similar to other biologics used for the treatment of psoriasis and therefore prescribers should be familiar with the monitoring and management of these risks. Based on the safety and efficacy demonstrated in clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. A Medication Guide will be part of labeling and will be used to convey risks to patients and instructions for use will communicate appropriate administration. Post-marketing requirements include a long-term prospective observational study which will provide additional real-world safety data.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Bimzelx (bimekizumab) is necessary to ensure the benefits outweigh its risks. UCB, Inc (hereafter referred to as the Applicant) submitted a

Biologics Licensing Application (BLA) 761151 for bimekizumab with the proposed indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. This application is under review in the Division of Dermatology and Dentistry. The Applicant did not submit a REMS with this application but submitted a risk management plan. The risk management plan proposed additional pharmacovigilance activities including plans to conduct a real-world outcomes study to further monitor the risks associated with bimekizumab, to establish a pregnancy registry, and to conduct a retrospective cohort study to evaluate exposure of bimekizumab in pregnancy. The Applicant also proposed a Medication Guide and instructions for use as part of labeling to convey the risks and proper administration.

2 Background

2.1 PRODUCT INFORMATION

Bimzelx (bimekizumab-bkzx, hereafter referred to as bimekizumab), a new molecular entity^a, is a humanized monoclonal antibody of immunoglobulin G1 (IgG1) that selectively binds to human interleukin-17A (IL-17A), interleukin 17F (IL-17F), and interleukin 17-AF cytokines, and inhibits their interaction with the receptor complex. Both IL-17A and IL17-F are cytokines involved in inflammatory and immune responses. By acting as an IL-17A and IL17F antagonist, bimekizumab inhibits the release of proinflammatory cytokines and chemokines. Bimekizumab is proposed for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.¹

Bimekizumab is proposed as a 160 mg/mL single-use prefilled syringe and a 160 mg/mL single-use autoinjector for subcutaneous (SC) injection. The proposed dosage regimen is 320 mg (two 160 mg SC injections) at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. The Applicant's initial labeling included the statement "for some patients, a dose of 320 mg every 4 weeks after week 16 may be considered". The review team revised the dosage regimen statement to "for some patients weighing ≥ 120 kg, a dose of 320 mg every 4 weeks after week 16 may be considered" for clarity.² Bimekizumab is proposed as chronic therapy for psoriasis and is likely to be administered by patients or caregivers in the outpatient setting.^b Bimekizumab was granted marketing authorization in the European Union and the United Kingdom in August 2021.

Three agents are approved in the United States for moderate to severe plaque psoriasis that target interleukin 17, Cosentyx (secukinumab), Taltz (ixekizumab), and Siliq (brodalumab). The risks associated with Cosentyx (secukinumab) and Taltz (ixekizumab) are infections, inflammatory bowel disease, and hypersensitivity reactions; these risks are communicated through labeling. However, Siliq (brodalumab) was approved with a REMS with elements to assure safe use to ensure the benefits outweigh the risk of

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

suicidal ideation and behavior. See Section 3.2 for additional information on safety and risk management for currently available treatment options for psoriasis.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761151 relevant to this review:

- **07/15/2020:** BLA 761151 submission for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy received.
- **12/17/2020:** A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for bimekizumab.
- **03/22/2021:** An information request was sent to the Applicant to gain more information about potential for drug-induced liver injury (DILI) with bimekizumab. The Agency requested that the Applicant establish a Hepatology Assessment Committee to evaluate subjects with bimekizumab who met Hy's Law or Temple's Corollary criteria.
- **04/13/2021:** A late-cycle meeting was held between the Agency and Applicant via teleconference. The Applicant updated the Agency that a Hepatology Assessment Committee was formed and was reviewing the cases. A full response to the Agency's IR was on track for submission by the agreed upon date. The Applicant was informed that REMS and risk management discussions remain under review pending the IR.
- **04/16/2021:** The Applicant submitted the IR response with the Hepatology Assessment Committee summary.
- **04/26/2021:** The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date 3 months.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations. The pathophysiology is complex and involves several cellular components and cytokines of the immune system. Psoriasis affects about 3% of the United States population.^{3,c} It can begin at any age, however, one population study of the age of onset revealed two peaks, at age 16 and at age 60. Plaque psoriasis is the most common form and accounts for about 85-90% of cases.⁴ It is characterized by well-demarcated, erythematous plaques with overlying coarse scale that typically affect the scalp, extensor elbows, knees and gluteal cleft.⁵ About 20% of patients have moderate to severe disease. Psoriasis is associated with comorbid conditions that include psoriatic arthritis, eye disorders, and other

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

disorders such as depression/suicide, cardiovascular disease, and metabolic syndrome.⁵ Moderate to severe plaque psoriasis has a substantial impact on patient quality of life. In addition to the physical manifestations, patients also report significant social and psychologic effects such as limitations on activities, depression, anxiety, embarrassment and stigma, and social discrimination.⁶ Psoriasis is also associated with increased overall mortality.^d Some deaths may be due to adverse effects from systemic therapies; however, psoriasis-related mortality may also be related to the risk of comorbid cardiovascular disease.⁵

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Currently approved drugs for the treatment of moderate to severe plaque psoriasis in adults include the antimetabolite methotrexate; tumor necrosis factor (TNF) inhibitors, such as etanercept, adalimumab, certolizumab pegol, and infliximab; IL-12 and IL-23 antagonist ustekinumab; IL-17A antagonists secukinumab and ixekizumab; IL-17A receptor antagonist brodalumab; IL-23 antagonists, guselkumab, tildrakizumab, and risankizumab; T-cell inhibitor cyclosporine (CSA); retinoid acitretin; and phosphodiesterase-4 (PDE-4) inhibitor apremilast. Phototherapy, with either PUVA (UVA light combined with the photosensitizer, psoralen methoxsalen) or UVB light therapy, is also a standard of care treatment for patients with moderate to severe plaque psoriasis. Phototherapy requires frequent office visits and carries an increased risk of squamous cell carcinoma of the skin. Topical agents are available but are not used as monotherapy for moderate to severe plaque psoriasis.

None of the available treatments provide a permanent cure or universal response. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI)^e, with the change from baseline as the most common primary efficacy endpoint. One meta-analysis of 60 clinical trials concluded that brodalumab, guselkumab, ixekizumab, and risankizumab were associated with the highest PASI response rates for both short and long-term efficacy.⁷ All agents are associated with at least one serious risk and risk management strategies vary (see Appendix 10.2 for Table 1). Treatment selection is individualized as it is necessary to consider patient-related factors such as presence of comorbidities or concomitant illness, treatment response or loss of response, and adverse event profiles of agents. Although several agents are available, there is additional need for agents for the treatment of moderate to severe plaque psoriasis.

Currently, Siliq (brodalumab) is the only biologic approved for moderate to severe plaque psoriasis that has risk mitigation strategies beyond labeling. The goal of the Siliq REMS is to mitigate the observed risk of suicidal ideation and behavior (SIB) including completed suicides, by ensuring that prescribers are

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^e The Psoriasis Area and Severity Index (PASI) is a measure of the average redness, thickness, and scaling (each graded on a 0-4 scale) of psoriatic lesions on four areas of the body (head, upper limbs, trunk, and lower limbs) weighted by the area of involvement using a 72-point scale, with the score of 72 representing maximal disease severity. PASI 90 stands for the status of achieving ≥90% reduction from baseline in the PASI score.

educated about the risk of SIB observed with brodalumab therapy and the need to counsel patients about this risk, and ensuring that patients are informed about the risk of SIB observed with therapy and the need to seek medical attention for manifestations of SIB, new onset or worsening depression, or other mood changes.

REMS were previously approved for the TNF inhibitors (etanercept, adalimumab, certolizumab pegol, and infliximab) and Stelara (ustekinumab). These REMS consisted of a Medication Guide and communication plan (CP) to address serious risks (see Appendix 10.2 for Table 1). The TNF inhibitors were released from REMS requirements in 2011 and ustekinumab was released in 2017 because the CP activities were completed, and the REMS assessments demonstrated that the REMS goals were being met. Medication Guides remain part of the labeling for these agents.

4 Benefit Assessment

The bimekizumab clinical development program included three pivotal phase 3 trials⁸, PS0008, PS0009, and PS0013 to evaluate the efficacy and safety of bimekizumab for the treatment of adult patients with moderate to severe plaque psoriasis who had the following: body surface area (BSA) involvement of $\geq 10\%$, an Investigator's Global Assessment^f (IGA) score of ≥ 3 ("moderate") in the overall assessment of psoriasis on a severity scale of 0 to 5, and a Psoriasis Area and Severity Index (PASI) score ≥ 12 . All three pivotal trials were multicenter, randomized, double-blind, placebo controlled (PS0009, PS0013) and/or active comparator controlled [PS0008 (adalimumab) and PS0009 (ustekinumab)]. The pivotal studies differed in study design and treatment assignment as described below.

PS0008 (National Controlled Trial (NCT) 03412747) was a multicenter, randomized, double-blind, parallel group, active-comparator-controlled (adalimumab) trial. The study included a screening period, 16-week initial treatment period, and a 40-week maintenance treatment period. Subjects were randomized 1:1:1 to receive bimekizumab 320 mg subcutaneously (SC) every 4 weeks, bimekizumab 320 mg every 4 weeks through week 16 then every 8 weeks through the maintenance period, or adalimumab^g therapy through week 24 followed by bimekizumab 320 mg every 4 weeks through the maintenance period.

PS0009 (National Controlled Trial (NCT) 03370133) was a multicenter, randomized, double-blind, parallel group, placebo and active-comparator-controlled (ustekinumab) trial. The trial included a screening period, 16-week initial treatment period, and a 36-week maintenance treatment period. Subjects were

^f The static investigator's global assessment was used to assess disease severity during the studies. The investigator assessed the overall severity of psoriasis using a 5-point scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe).

^g Adalimumab 80 mg as an initial dose followed by 40 mg every other week starting 1 week after the initial dose through week 24.

randomized 4:2:1 to bimekizumab 320 mg SC every 4 weeks, ustekinumab^h therapy, or placebo administered every 4 weeks through week 16 followed by bimekizumab 320 mg every 4 weeks.

PS0013 (NCT 03410992) was a randomized, double-blind, placebo-controlled trial. The trial included a screening period, 16-week placebo-controlled initial treatment period, followed by a 40-week randomized withdrawal period. Subjects were randomized 4:1 to bimekizumab 320 every 4 weeks or placebo. At week 16, subjects who achieved a PASI 90 response continued into the 40-week randomized withdrawal period. In this period, subjects originally randomized to bimekizumab were re-randomized (1:1:1) to either bimekizumab 320 mg every 4 weeks, bimekizumab 320 every 8 weeks, or placebo. Subjects in the placebo group continued placebo if they achieved a PASI 90 response. Subjects who did not achieve a PASI90 response at week 16 entered an open-label escape arm and received bimekizumab 320 mg every 4 weeks for 12 weeks. Participants who relapsed (defined as not achieving a PASI75 response) during the randomized withdrawal period also entered the 12-week escape arm.

The co-primary efficacy endpoints included the proportion of subjects who achieved an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline to Week 16 and the proportion of subjects who achieved at least a 90% reduction in PASI score (PASI 90) from baseline to Week 16. Secondary endpoints included various PASI and IGA responses at several timepoints and other measures.

After completion of the maintenance treatment periods of the pivotal studies, eligible subjects could continue into PS0014, an open label study to assess long-term efficacy and safety of bimekizumab or were required to complete a safety follow up visit 20 weeks after the last study dose.

Results:

The review team determined the primary efficacy data to support approval of bimekizumab was the placebo-controlled data in the 16-week treatment period from pivotal studies PS0009 and PS00013. Bimekizumab was statistically superior to placebo for both co-primary endpoints at week 16 in both trials. Several secondary endpoints were evaluated and showed a statistically significant difference for bimekizumab treatment compared to placebo (See Table 1).

^h Ustekinumab therapy was dosed based on weight. Subjects ≤100 kg at baseline received 45 mg initially and 4 weeks later, then every 12 weeks. Subjects >100 kg at baseline received 90 mg initially and 4 weeks later, then every 12 weeks. Efficacy data comparing bimekizumab to ustekinumab will not appear in the labeling.

Table 1. Results for the Co-Primary Endpoint at Week 16 in PS0009 and PS0013⁶

	PS0009		PS0013	
	Bimekizumab	Placebo	Bimekizumab	PBO
Randomized subjects¹	N=321	N=83	N=349	N=86
IGA 0/1	270 (84%)	4 (5%)	323 (93%)	1 (1%)
Difference from Placebo (95% CI)²	79% (73%, 85%)		91% (88%, 95%)	
P-Value²	<0.001		<0.001	
PASI-90 at Week 16	273 (85%)	4 (5%)	317 (91%)	1 (1%)
Difference from Placebo (95% CI)²	80% (74%, 86%)		90% (86%, 93%)	
P-Value²	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Abbreviations: BKZ=bimekizumab; PBO=placebo

¹ Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

² Estimate, 95% confidence interval (CI) and p-value for the difference are based on CMH test stratified for region and prior biologic use

Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.

Trial PS0008 and PS0009 included active comparator arms; however, the Applicant did not provide an adequate scientific bridge between European Union approved and US licensed active controls used. In both trials, bimekizumab was statistically superior to the active control in the overall population and US-sourced subgroup.⁶ The review team determined the data was supportive (b) (4).

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for the intended use in the target population.^{i,6}

5 Risk Assessment & Safe-Use Conditions

A total of 1789 subjects with moderate to severe plaque psoriasis received bimekizumab in the clinical development program, with 1371 subjects treated for greater than 12 months.^{9,10} The primary review of safety of bimekizumab for the treatment of moderate to severe plaque psoriasis focused on pooled data from phase 3 trials. Long-term safety data were provided by phase 3, open-label, long term extension Trial PS0014. Several phase 2 trials provided supportive safety data (PS0010, PS0011, PS0016, and PS0018), and two clinical use trials evaluated the ability of subjects to perform self-injection of the proposed safety syringe and auto-injector.

The review team used the following pools for the safety analysis⁶:

- Pool S1: The primary analysis for review of safety included pooled data from Initial Treatment Period (Week 0-16) placebo-controlled period of pivotal studies PS0009 and PS0013 [bimekizumab-treated subjects (N=670) and placebo (N=169)].

ⁱ Section 505-1(a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

- Pool S2B: The pool consisted of data from the Maintenance Period of Trials PS0009 and PS0013 and supported the analysis of safety through Week 56. This pool included 488 subjects treated with bimekizumab 320 mg Q4W and 103 subjects treated with bimekizumab 320 mg Q8W.
- Pool S2C: The pool consisted of data from the Maintenance Period of Trials PS0008 and PS0013 and supported the analysis of the comparative safety of the Q4W and Q8W dosing regimens. This pool consisted of 261 subjects treated with bimekizumab 320 mg Q4W and 257 subjects treated with bimekizumab 320 mg Q8W.

Active comparators were included in PS0008 and PS0009. The clinical team evaluated the comparative safety data against active comparators in the individual trials. However, the Applicant did not establish a scientific bridge between US-licensed and EU-approved products, (b) (4)

The most common adverse reactions ($\geq 1\%$ in bimekizumab and reported more frequently than placebo) were upper respiratory tract infections (15%), candida infections (10%), headache (3%), injection site reactions (3%), tinea infections (1%), herpes simplex infections (1%), acne (1%), and folliculitis (1%). The most common system organ class (SOCs) for adverse events leading to discontinuation during the placebo-controlled periods in the bimekizumab group were Infections and Infestations (3/670, 0.4%), Skin and Subcutaneous Disorders (2/670, 0.3%), and Investigations^j (2/670, 0.3%).

5.1 DEATHS

There were 5 deaths reported in subjects treated with bimekizumab and 1 death in each of the placebo and active comparator arms.⁹ The causes of death in the five bimekizumab-treated subjects were respiratory and circulatory failure, hypovolemic shock secondary to an upper gastrointestinal hemorrhage related to an alcohol binge episode, two events adjudicated as MACE [sudden cardiac arrest (N=1) and cardiopulmonary failure/acute cardiorespiratory failure (N=1)], and death from an unknown cause^k. One additional death, a fatal myocardial infarction adjudicated as MACE, was reported in the 120-Day Safety Update in Trial PS0014.¹⁰ The Applicant concluded that none of the deaths were determined to be drug-related.^{9,10} The clinical reviewer concluded that treatment with bimekizumab did not appear to increase the risk of mortality.⁶

^j According to the Medical Dictionary for Regulatory Activities, the System Organ Class of Investigations includes clinical laboratory tests, biopsies, radiologic tests, physical examination parameter, or physiologic test (e.g. decreased blood pressure). The preferred terms within the SOC Investigations only represent the result and not a specific clinical condition.

^k Patient was withdrawn from the trial PS0009 at Week 24 due to noncompliance and refusal for treatment of nonserious cellulitis event. The death was reported 3 months later. No additional information was available.

5.2 SERIOUS ADVERSE EVENTS^{l,m}

In Pool S1, serious adverse events (SAE) were reported in 11/670 (1.6%, EAIR 5.3/100 subject-years) bimekizumab-treated subjects and 4/169 (2.4%, EAIR 5.3/100 subject-years) placebo-treated subjects. In the bimekizumab group the most common serious adverse events were in the SOC of gastrointestinal disorders (3/670, 0.4%), infections and infestations (2/670, 0.3%), and musculoskeletal and connective tissue disorders (2/670, 0.3%). No serious adverse event was reported by greater than 1 participant in either treatment group. In Pool S2B (maintenance period of PS0009 and PS0013), SAEs were reported in 23/488 (4.7%, EAIR 7.0/100 subject-years) subjects treated with bimekizumab Q4W. The clinical reviewer reviewed the safety data for every 4-week dosing compared to every 8-week dosing regimens (Pool S2C). In Pool S2C, SAEs were reported by 8/261 (3.1%) of subjects treated with the Q4W regimen and 11/257 (4.3%) of subjects treated with the Q8W regimen. The most common SOC in which SAEs were reported in the Q4W group was Infections and Infestations (2/261, 0.8%, EAIR 1.0/100 subject-years). The most common SOCs in which SAEs were reported in the Q8W group were GI disorders (4/257, 1.6%, EAIR 2.1/100 subject-years) and Infections and Infestations (2/257, 0.8%, EAIR 1.0/100 subject-years).

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

Several adverse events of interest were identified prospectively in the clinical development program based on the psoriasis patient population and mechanism of action of bimekizumab or related agents. Similar to other biologics used for psoriasis, the risk of infections and the risk of tuberculosis will be communicated via labeling in Section 5 - Warnings and Precautions. In addition, labeling will include the recommendation to evaluate for tuberculosis infection prior to initiating treatment in Section 2 - New onset inflammatory bowel disease and exacerbation of pre-existing inflammatory bowel disease have been reported with IL-17 inhibitors in patients with psoriasis. The GI consult reviewer recommends the risk of inflammatory bowel disease be communicated in Section 5 - Warnings and Precautions.¹¹ Similar to other immunosuppressants, increased risk of malignancy is an adverse event of interest. Because of the long latency period, this risk will be evaluated in a prospective long-term safety which will be a post-marketing requirement (PMR).⁶ A Division of Cardiology and Nephrology consult reviewer evaluated the

^l Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

^m Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug*

cases of major adverse cardiovascular events (MACE)ⁿ and concluded that no labeling for MACE is necessary for bimekizumab.¹²

5.3.1 Drug-Induced Liver Injury

During the review of safety data, the clinical team identified imbalances in liver enzyme elevations (liver biochemical abnormalities) and potential cases of drug-induced liver injury associated with bimekizumab. This safety signal was evaluated by the review team in conjunction with a consult by the Division of Hepatology and Nutrition (DHN), Drug-Induced Liver Injury Team. Additionally, the review team issued an IR to request the Applicant convene an independent Hepatology Assessment Committee to evaluate subjects with bimekizumab who met Hy's Law or Temple's Corollary criteria. The Committee reviewed all cases of ALT or AST elevations greater than 5 times the upper limit of normal (ULN) and performed a causality assessment. The Committee concluded they did not detect a significant liver safety concern with bimekizumab.¹³

The DHN reviewer evaluated liver enzyme abnormalities in Pool S1 and Pool S2 (pooled data from the phase 2 and phase 3 trials). The DHN consult reviewer noted an imbalance in elevation of transaminases with more occurring in bimekizumab treatment arms compared to placebo. In Pool S1, liver enzyme elevations greater than 3x the ULN occurred in 3.4% of bimekizumab treated patients compared to 1.8% of placebo-treated patients. In Pool S2, the median percentage of patients with liver enzyme elevations 2-5x the ULN was 7.5% (range 4.1-18.6) across bimekizumab arms compared to 4.5% in the placebo group. The median percentage of patients with liver enzyme elevations 5-10x ULN was 0.3% (range 0-4.7%) across bimekizumab compared to 0% for placebo. There was not a clear dose-response relationship. Bimekizumab arms had higher rates of hepatic treatment emergent adverse events per 100-patient years of exposure compared to the active treatment arms in the trials. The reviewer assessed all bimekizumab cases in the Hy's Law quadrant or ALT >5x ULN regardless of bilirubin (N=30). Out of the 30, 3 were considered probable DILI and 7 were considered possible DILI by the consultant reviewer. There were no deaths or liver transplants, no definite or probable Hy's Law cases, nor was a clear DILI phenotype observed. The DHN consult reviewer concluded that the risk of DILI can be managed with labeling and routine post-market surveillance.¹⁴

The review team, including the DHN consultant, recommend the risk of liver biochemical abnormalities be communicated in labeling.^{6,14} This risk will be conveyed in Section 5, Warnings and Precautions. The warning will include information about the need for baseline and periodic monitoring of liver enzymes, alkaline phosphatase, and bilirubin during treatment, to interrupt treatment and evaluate for DILI if increased liver enzymes occur, and to discontinue treatment permanently if elevations are determined to be causally associated. In addition, labeling will include a limitation of use that bimekizumab is not recommended in patients with active liver disease, cirrhosis, (b) (4) because of an

ⁿ MACE was defined as CV death, non-fatal myocardial infarction (MI), or stroke. Extended MACE was defined as all MACE plus adjudicated event types of hospitalization for unstable angina with urgent revascularization, hospitalization for heart failure, transient ischemic attack, coronary revascularization procedures

increased risk of severe hepatic injury. The need for baseline assessment of liver enzymes, alkaline phosphatase, and bilirubin prior to initiation will be conveyed in Section 2.1 of the label. If approved, this risk will be an outcome of interest in the post-marketing safety study which will be a PMR.

5.3.2 Suicidal Ideation and Behaviors

Suicidal ideation was an adverse event of interest in the clinical development program for bimekizumab because the risk of SIB is higher in patients with psoriasis than the general population and because brodalumab (another agent targeting IL 17) is subject to a REMS due to the increased risk of SIB. Trial protocols included proactive surveillance for SIB. DDD consulted the Division of Psychiatry (DP) to review the psychiatric adverse events, suicidal ideation and behavior, depression, and anxiety from the phase 2 and phase 3 clinical trials.¹⁵ The DP consult reviewer concluded the incidence of psychiatric events was numerically low (<2%) in bimekizumab-treated subjects during the initial placebo or active-controlled treatment period. The suicidal ideation and behavior incidence was $\leq 2\%$ for bimekizumab (exposure adjusted incidence rate for adjudicated suicidal ideation/behavior was 0.07 per 100 patient years) and the reviewer noted this was similar to the background incidence for suicidal ideation and behavior in this population. There were no deaths or suicidal behavior events in any patient in the clinical development program. The DP consult reviewer does not recommend specific psychiatric warning language for bimekizumab labeling based on the data available.

6 Expected Postmarket Use

Bimekizumab is likely to be prescribed by dermatologists and is expected to primarily be used by patients in the outpatient setting. Bimekizumab is proposed to be available as a prefilled syringe or autoinjector. The product is intended to be administered subcutaneously by self-injection, a caregiver, or a healthcare professional. Healthcare professionals will need to provide proper training to patients and/or caregivers on preparation, administration, and dose according to the Instructions for Use included in the labeling. If approved, bimekizumab will be the fourth psoriasis agent that targets the IL-17 pathway and one of several biologic agents. Approved products for the treatment of psoriasis have a similar risk profile, therefore healthcare providers who are likely to prescribe bimekizumab should be familiar with the risks.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS with this application but submitted a risk management plan. The risk management plan proposed additional pharmacovigilance activities including plans to conduct a real-world outcomes study to further monitor the risks associated with bimekizumab, to establish a pregnancy registry, and to conduct a retrospective cohort study to evaluate exposure of bimekizumab in

pregnancy. The Applicant also proposed a Medication Guide and instructions for use as part of labeling to convey the risks.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of bimekizumab on the basis of the efficacy and safety information currently available.

Moderate to severe plaque psoriasis is a serious and, at times, disabling condition that has substantial impact on patients' lives. The benefit of bimekizumab for the treatment of moderate to severe plaque psoriasis was demonstrated in two pivotal phase 3 placebo-controlled trials, PS0009 and PS00013. Bimekizumab was statistically superior to placebo for the co-primary endpoints at week 16 in both trials.

A safety concern with bimekizumab is the possible risk of drug-induced liver injury which was identified by the review team after the midcycle meeting. The risk of DILI was evaluated by the review team in conjunction with a DHN consult. In clinical trials, there were imbalances in liver enzyme elevations; however, there were no definite or probable Hy's Law cases, liver transplants, or deaths. Drug-induced liver injury has not been reported with other IL-17 inhibitors; however, it has been associated with other agents for the treatment of psoriasis. The proposed bimekizumab labeling communicates the risk of liver biochemical abnormalities and recommends monitoring of liver enzymes, alkaline phosphatase, and bilirubin prior to treatment initiation and periodically throughout therapy. Additionally, the label includes a limitation of use statement to avoid bimekizumab in patients with active liver disease, cirrhosis, or excessive alcohol use as these patients may be at increased risk for severe hepatic injury. Additional safety concerns for bimekizumab are similar to other agents for moderate to severe plaque psoriasis and include the risk of infections, reactivation of tuberculosis, inflammatory bowel disease, and avoiding the use of live vaccines during treatment. The healthcare providers who are likely to prescribe bimekizumab should be familiar with treatment regimens that include immunomodulator agents that block cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-17, and the risks associated with these treatments. Additionally, the biologics infliximab, adalimumab, etanercept, and ustekinumab, which had REMS programs to mitigate the risks of infections and malignancies, had their REMS released after the REMS communication plan activities were completed and the assessments showed that healthcare professionals understood the key messages. For these agents, no risk mitigation strategies beyond labeling are used to communicate these risks. We anticipate the likely prescribers for bimekizumab will be aware and knowledgeable about the class risks associated with biologic agents used for the treatment of psoriasis.

Therefore, based on the data currently available, this reviewer is not recommending a REMS for the risks of bimekizumab. The risks will be conveyed with labeling, including a Medication Guide. Additionally, post-marketing requirements include a long-term prospective observational study to assess the risk of malignancy and other serious adverse reactions (e.g., serious infection [including opportunistic infection], reactivation of Hepatitis B, tuberculosis, gastrointestinal [including inflammatory bowel disease, elevated liver enzymes/hepatotoxicity], cardiovascular, and hematologic events).

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. In general, healthcare providers who treat moderate to severe plaque psoriasis are likely familiar with the risk of drug-induced liver injury and liver enzyme elevations, infections, IBD, and the importance of monitoring. At the time of this review, labeling negotiations were ongoing. Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 REFERENCES

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10.2 TABLE 1. BIOLOGIC THERAPIES APPROVED IN THE US FOR MODERATE TO SEVERE PLAQUE PSORIASIS

Name (Generic), Approval Year <i>Drug class</i>	Route	Safety issues	Risk Management Approaches: REMS, Boxed Warning, Medication guide
Enbrel (etanercept), 1998 <i>TNF inhibitor</i>	Injection, subcutaneous	Serious infections, malignancies, invasive fungal infections, neurologic reactions, heart failure, hematologic reactions, allergic reactions, autoimmunity	- REMS with medication guide and communication plan approved in 2008 for risk of serious infections - REMS released in 2011 - Boxed Warning for serious infections and malignancies - Medication Guide
Remicade (infliximab), 1999 <i>TNF inhibitor</i>	Injection, intravenous infusion	Serious infections, invasive fungal infections, malignancies, hepatitis B virus reactivation, hepatotoxicity, heart failure, cytopenias, hypersensitivity, cardiovascular and cerebrovascular reactions, demyelinating disease, lupus- like syndrome	- REMS with medication guide and communication plan approved in 2009 for risk of serious infections - REMS released in 2011 - Boxed Warning for serious infections and malignancy - Medication Guide
Humira (adalimumab) 2002 <i>TNF inhibitor</i>	Injection, subcutaneous	Serious infections, invasive fungal infections, malignancies, anaphylaxis or serious allergic reactions, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, lupus-like syndrome	- REMS with medication guide and communication plan approved in 2010 for risk of serious infections - REMS released in 2011 - Boxed Warning for serious infections and malignancy - Medication Guide
Cimzia (certolizumab) 2008 ^o <i>TNF inhibitor</i>	Injection, subcutaneous	Serious infections, malignancies, heart failure, hypersensitivity reactions, hepatitis B virus reactivation, neurologic reactions, hematological reactions, autoimmunity	- REMS with medication guide and communication plan approved for risk of serious infections, malignancies, psoriasis-like lesions - REMS released in 2011 - Boxed Warning for serious infections and malignancy - Medication Guide

^o The indication for moderate to severe plaque psoriasis was approved in 2018

Stelara (ustekinumab) 2009 <i>IL-12 and IL-23 antagonist</i>	Injection, subcutaneous ^p	Infections, malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy, noninfectious pneumonia	- REMS with medication guide and communication plan for risk of serious infections, malignancies, reversible posterior leukoencephalopathy - REMS released in 2017 - No Boxed Warning - Medication Guide
Cosentyx (secukinumab), 2015 <i>Anti-IL-17A antibody</i>	Injection, subcutaneous	Infections, inflammatory bowel disease, hypersensitivity reactions	- No REMS or Boxed Warnings - Medication Guide
Taltz (ixekizumab) 2016 <i>Anti-IL-17A antibody</i>	Injection, subcutaneous	Infections, hypersensitivity, inflammatory bowel disease	- No REMS or Boxed Warnings - Medication Guide
Siliq (brodalumab) 2017 <i>IL-17A receptor antagonist</i>	Injection, subcutaneous	Suicidal ideation and behavior, infections, Crohn's disease	- REMS with ETASU for the risk of suicidal ideation and behavior (SIB) - Boxed Warning for SIB - Medication Guide
Tremfya (guselkumab), 2017 <i>Interleukin 23 Antagonist</i>	Injection, subcutaneous	Hypersensitivity, infections	- No REMS or Boxed Warnings - Medication Guide
Ilumya (tildrakizumab), 2018 <i>Interleukin 23 Antagonist</i>	Injection, subcutaneous	Hypersensitivity, infections	- No REMS or Boxed Warnings - Medication Guide
Skyrizi (risankizumab) 2019 <i>Interleukin 23 Antagonist</i>	Injection, subcutaneous	Infections	- No REMS or Boxed Warnings - Medication Guide

^p Available as subcutaneous injection and injection for intravenous infusion. The subcutaneous injection is approved for the psoriasis indications.

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