CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761061Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	761061
PDUFA Goal Date	July 16, 2017
OSE RCM #	2016-2620, 2016-2622
Reviewer Name(s)	Laura Zendel, PharmD, BCPS, Division of Risk Management (DRISK)
Team Leader	Donella Fitzgerald, PharmD, DRISK
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Review Completion Date	June 27, 2017
Subject	Evaluation of Need for a REMS
Established Name	guselkumab
Trade Name	Tremfya
Name of Sponsor	Janssen Biotech, Inc.
Therapeutic Class	Human Interleukin 23 Antagonist
Formulation(s)	100 mg/ml single-dose prefilled syringe
Dosing Regimen	100mg administered by subcutaneous injection at week 0, week 4, and every 8 weeks thereafter

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Executive Summary

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tremfya (guselkumab) is necessary to ensure the benefits of this product outweigh its risks. Janssen Research and Development, LLC submitted a Biologic Licensing Application (BLA 761061) for guselkumab with the proposed indication of the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The risk associated with the use of guselkumab includes infections. The Sponsor did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Dermatology and Dental Products agree that a REMS is not needed to ensure the benefits of guselkumab outweigh its risks. Guselkumab has proven to reduce the severity of symptoms in patients with moderate-to-severe plaque psoriasis. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. In general, healthcare providers who treat psoriasis should be familiar with the risk of infections.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tremfya (guselkumab) is necessary to ensure the benefits of this product outweigh its risks. Janssen Research and Development, LLC (JRD) submitted a Biologic Licensing Application (BLA 761061) for guselkumab on November 16, 2016 for the proposed indication of the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This application is under review in the Division of Dermatology and Dental Products (DDDP). The Sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Guselkumab, a new molecular entity,[a] is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 subunit of interleukin-23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines. Guselkumab is proposed for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Guselkumab is proposed to be available as 100mg/ml prefilled syringes to be administered by subcutaneous route at week 0, week 4, and every 8 weeks thereafter.[b] It may be administered by a

[a] FDAAA factor (F): Whether the drug is a new molecular entity

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug

healthcare professional, or a patient may self-inject after proper training in subcutaneous injection technique.

Guselkumab was granted priority review status due to the sponsor's use of a Tropical Disease Priority Review Voucher, PRV 204384, granted on December 28, 2012 for NDA 204348 for Sirturo (bedaquiline) 100mg tablets as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis.

Guselkumab is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761061 relevant to this review:

- 4/6/2016: A preliminary discussion on the need for a REMS was held at the pre-BLA meeting. The Agency informed the Sponsor that based on the information available at the time, a REMS would likely not be necessary for guselkumab.
- 9/6/2016: Information Request sent by the Agency requested that the Sponsor conduct a retrospective evaluation of suicidal ideation and behavior (SIB) using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects enrolled in guselkumab clinical trials and include analysis with the BLA submission due to the risk of SIB found with brodalumab, another interleukin receptor antagonist that is approved for the treatment of adult patients with moderate-to-severe plaque psoriasis.
- 11/16/2016: BLA 761061 submission for guselkumab injection indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy received. A priority review was subsequently granted.
- 3/8/2017: A Mid-cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on the currently available data, there were no safety issues that require a REMS for guselkumab.
- 5/16/2017: A Late-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on the currently available data, there were no safety issues that require a REMS for guselkumab.

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. It can present in many different patterns from the scalp to the feet and cause psychiatric distress and physical disabilities. Psoriasis affects approximately 2-3% of the U.S. population. It can begin at any age, but one population study of the age of onset revealed two peaks, at age 16 and at age 60. Risk factors may include family history, obesity, smoking and environmental smoke, and heavy alcohol use. Risk factors that may trigger or exacerbate psoriasis include stress, physical trauma to the skin, cold dry weather, sun exposure and hot weather, infections, and certain medications. Moderate-

to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patient's lives.[1,2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Multiple products are approved for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

Currently approved drugs for the treatment of moderate-to-severe psoriasis include the anti-metabolite methotrexate (MTX), tumor necrosis factor (TNF) inhibitors, such as etanercept, adalimumab and infliximab, IL-12+23 antagonist ustekinumab, IL-17A antagonists secukinumab and ixekizumab, IL-17A receptor antagonist brodalumab, T-cell inhibitor cyclosporine (CSA), retinoid acitretin, and phosphodiesterase-4 (PDE-4) inhibitor apremilast (see Appendix 11.2). Phototherapy, with either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy, is also a standard of care treatment for moderate-to-severe psoriasis patients. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI), with the change from baseline as the most common primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75 $\geq$ 70%) for cyclosporine, infliximab, adalimumab, ustekinumab and secukinumab to moderately efficacious (PASI 75 $\geq$ 40%) for methotrexate and etanercept, to somewhat efficacious (PASI 75 $\geq$ 20%) for acitretin and apremilast.**Error! Bookmark not defined.**

Infliximab, etanercept, and adalimumab were all approved with a REMS that consisted of a Medication Guide (MG) and communication plan (CP) to address the risks of infections and malignancies. All three drugs were released from their CP REMS requirement in 2011 because the CP activities were completed and the REMS assessments demonstrated that the REMS goals were being met. The MG remains a part of the labeling for each of these products.

The ustekinumab REMS was originally approved in 2009 with a MG, CP, and timetable for assessments. The REMS was required to address the risks of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS). The Agency approved a modification on May 2, 2012 to remove the MG from the REMS and retain it as part of the approved labeling. The 3-Year and 7-Year REMS assessments concluded that the ustekinumab REMS was meeting its goals of evaluating and mitigating potential risks of serious infections, malignancy, and RPLS by alerting and warning healthcare providers.[3,4] The Agency approved a second modification on September 20, 2013 to update the REMS materials to include information for a new indication of psoriatic arthritis (PsA), and added rheumatologists as a new target prescriber population. Therefore, an evaluation of rheumatologists' understanding of the risks was added as a part of the assessment plan. The timetable for submission of assessments was not changed. The CP activities for ustekinumab were completed in September 2014, and rheumatologists' knowledge of the risks was assessed in the 7-Year REMS assessment report. The

Sponsor for ustekinumab submitted a REMS Modification requesting release from the CP REMS on December 16, 2016. The Agency subsequently released the REMS on February 15, 2017.

Siliq (brodalumab), an IL-17A receptor antagonist, is the most recently approved treatment for moderate-to-severe plaque psoriasis. Brodalumab was approved on February 15, 2017 with a REMS consisting of elements to assure safe use (ETASU) and a timetable for submission of assessments. A MG is also included as part of the approved labeling. The ETASU includes 1) healthcare providers who prescribe brodalumab are specially certified, 2) pharmacies that dispense brodalumab are specially certified, and 3) brodalumab can only be dispensed to patients with evidence or other documentation of safe-use conditions. The goal of the Siliq REMS is to mitigate the observed risk of suicidal ideation and behavior (SIB) including completed suicides, which occurred in subjects treated with Siliq by: 1) ensuring that prescribers are educated about the risk of SIB observed with Siliq therapy and the need to counsel patients about this risk and 2) ensuring that patients are informed about the risk of SIB observed with Siliq therapy and the need to seek medical attention for manifestations of SIB, new onset or worsening depression, or other mood changes.

4 Benefit Assessment

Evidence of the effectiveness of guselkumab for the treatment of moderate-to-severe plaque psoriasis in adult patients was derived from two pivotal trials, PSO3001 (Voyage 1) and PSO3002 (Voyage 2). Patients 18 years of age and older with moderate-to-severe plaque psoriasis (with or without PsA) for at least six months who were candidates for phototherapy or systemic therapy were eligible for enrollment. Moderate-to-severe plaque-type psoriasis was defined by Investigator's Global Assessment (IGA) $\geq$ 3 ("moderate") on a 5-point scale of overall disease severity, PASI $\geq$ 12, and a minimum affected body surface area (BSA) of 10%. Subjects with non-plaque forms of psoriasis or with drug-induced psoriasis were excluded as well as those who had ever received guselkumab or adalimumab (the comparator). The investigators used both US-licensed and non-US-licensed adalimumab in the studies, but did not provide bioequivalence data for the non-US-licensed product. Therefore, only data from US-licensed adalimumab will be considered.

Safety data was considered from an additional Phase 3 study, PSO3003 (Navigate), and a Phase 2 study, PSO2001.

In both VOYAGE 1 and VOYAGE 2, subjects were randomized to either guselkumab (100mg at Weeks 0 and 4, then every 8 weeks thereafter), placebo, or adalimumab (80mg at Week 0 and 40mg at Week 1, followed by 40 mg every 2 weeks thereafter). The co-primary endpoints were 1) the proportion of subjects who achieved an IGA score of 0 ("clear") or 1 ("minimal") and 2) the proportion of subjects who achieved at least a 90% reduction on the PASI composite score (PASI 90), both assessed at Week 16.

Comparisons between guselkumab and adalimumab were assessed as secondary endpoints in both studies at Week 16, the proportions of subjects who achieved an IGA score of 0 or 1, a PASI 90, and a PASI 75 response, and at Weeks 24 and Week 48 (VOYAGE 1 only), the proportions of subjects achieving an IGA score of 0, an IGA score of 0 or 1, and a PASI 90 response. Other outcomes evaluated included

improvement in psoriasis symptoms as assessed on the Psoriasis Symptoms and Signs Diary[5] (PSSD)[c] and improvements in psoriasis of the scalp at Week 16.

Results of VOYAGE 1 and VOYAGE 2

In both studies, a total of 1443 subjects were randomized to either guselkumab, placebo, or US licensed adalimumab. A summary of clinical responses for Week 16, Week 24, and Week 48 are presented in Tables 1 and 2. The Sponsor concluded, that there were substantial, significant, and clinically meaningful improvements in psoriasis compared with placebo through Week 16 and superior efficacy in skin, scalp, hand and foot psoriasis as well as patient-reported outcomes compared with adalimumab across multiple endpoints and time points through Week 48. Guselkumab demonstrated significant improvement in psoriasis as measured by PASI and IGA, by regional psoriasis measures[d] and patient-reported outcomes.[e] The clinical reviewer agrees that in Voyage 1 and Voyage 2, guselkumab was superior to placebo in both IGA and PASI 90 at Week 16. Comparisons between guselkumab and US licensed adalimumab were assessed as secondary endpoints at Week 16 and Week 24 and the results of an analysis of all the North America sites (US and Canada) demonstrate superiority of guselkumab to US licensed adalimumab. Greater improvements were observed in symptoms of psoriasis (itch, pain, stinging, burning, and skin tightness) at Week 16 in guselkumab compared to placebo in both trials based on the PSSD. Greater proportions of subjects on guselkumab compared to US licensed adalimumab achieved a PSSD symptom score of 0 (symptom-free) at Week 24 in both trials. Examination of age, gender, race, body weight, and previous treatment with systemic or biologic agents did not identify differences in response to guselkumab.

To evaluate maintenance and durability of response (VOYAGE 2), subjects randomized to guselkumab at Week 0 and who were PASI 90 responders at Week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or withdrawn from therapy (i.e. placebo). At Week 48, 89% of subjects who continued on guselkumab achieved PASI 90 compared to 37% of subjects who were re-randomized to placebo and withdrawn from guselkumab. For responders at Week 28 who were re-randomized to placebo and withdrawn from guselkumab, the median time to loss of PASI 90 was approximately 15 weeks.

[c] The PSSD evaluates the following symptoms: itch, pain, stinging, burning, and skin tightness. Qualitative data supports the importance and relevance of these symptoms from the patient's perspective. A Clinical Outcome Assessment review concluded that based on the Sponsor's qualitative and quantitative evidence presented, the PSSD appropriately measures symptom severity and appears to be fit for the purpose of the drug development program.

[d] Fingernail Physician's Global Assessment (f-PGA), Nail Psoriasis Area and Severity Index (NAPSI), scalp-specific Investigator's Global Assessment (ss-IGA), Physician's Global Assessment of hands and/or feet (hf-PGA)

[e] Dermatology Life Quality Index (DLQI), Psoriasis Symptom and Sign Diary (PSSD), Hospital Anxiety and Depression Scale (HADS), Work Limitations Questionnaire (WLQ), Medical Outcomes Study 36-Item Short Form (SF-36)

4.1 TABLE 1: CO-PRIMARY ENDPOINTS AT WEEK 16

	VOYAGE 1			VOYAGE 2		
	Guselkumab (N=329) n (%)	Placebo (N=174) n (%)	P-Value	Guselkumab (N=496) n (%)	Placebo (N=248) n (%)	P-Value
IGA response of 0/1	280 (85)	12 (7)	<0.001	417 (84)	21 (8)	<0.001
PASI 90 response	241 (73)	5 (3)	<0.001	347 (70)	6 (2)	<0.001

4.2 TABLE 2: EFFICACY RESULTS IN ADULTS WITH PSORIASIS

	Voyage 1				Voyage 2			
	Placebo N = 174 N_{US} = 62	Guselkumab N = 329 N_{US} = 115	Adalimumab N = 334 N_{US} = 115	P-Value	Placebo N = 248 N_{US} = 79	Guselkumab N = 496 N_{US} = 160	Adalimumab N = 248 N_{US} = 81	P-Value
	PASI 75 Response							
Week 16 N (%)	10 (5.7%)	300 (91.2%)	244 (73%)	<0.001	20 (8.1%)	428 (86.3%)	170 (69%)	<0.001
N_{US} (%)	1 (2%)	104 (91%)	80 (70%)	<0.001	7 (9%)	132 (83%)	51 (63%)	<0.001
	PASI 90 Response							
Week 16 N (%)	5 (2.9%)	241 (73.1%)	166 (50%)	<0.001	6 (2.4%)	347 (70.0%)	116 (47%)	<0.001
N_{US} (%)	1 (2%)	84 (73%)	47 (41%)	<0.001	(4%)	(64%)	(42%)	<0.001
Week 24 N (%)	N/A	264 (80.2%)	177 (53%)	<0.001	N/A	373 (75.2%)	136 (55%)	<0.001
N_{US} (%)		92 (80%)	50 (44%)	<0.001		113 (71%)	41 (51%)	0.003
Week 48 N (%)	N/A	251 (76.3%)	160 (48%)	<0.001	N/A	N/A	N/A	
N_{US} (%)		83 (73%)	52 (46%)	<0.001				
	IGA Response of 0/1 (cleared or minimal)							
Week 16 N (%)	12 (6.9%)	280 (85.1%)	219 (66%)	<0.001	21 (8.5%)	417 (84.1%)	168 (68%)	<0.001
N_{US} (%)	2 (3%)	96 (84%)	70 (61%)	<0.001	(6%)	118 (74%)	50 (62%)	0.027
Week 24 N (%)	N/A	277 (84.2%)	205 (61%)	<0.001	N/A	414 (83.5%)	161 (65%)	<0.001
N_{US} (%)		96 (84%)	62 (54%)	<0.001		118 (74%)	46 (57%)	0.005
Week 48 N (%)	N/A	265 (80.5%)	184 (55%)	<0.001	N/A	N/A	N/A	
N_{US} (%)		90 (79%)	62 (54%)	<0.001				
	IGA Response of 0 (cleared)							
Week 24 N (%)	N/A	173 (52.6%)	98 (29%)	<0.001	N/A	257 (51.8%)	78 (31%)	<0.001
N_{US} (%)		61 (53%)	26 (23%)	<0.001		76 (48%)	22 (28%)	0.005
Week 48 N (%)	N/A	166 (50.5%)	86 (26%)	<0.001	N/A	N/A	N/A	
N_{US} (%)		57 (50%)	27 (24%)	<0.001				
	PSSD Score of 0							
Week 24	N = 129	N = 248	N = 273		N = 198	N = 410	N = 200	
Overall	11%	36%			13%	35%		

US + Canada	13%	37%	26%		13%	43%	25%	
	Change from baseline Dermatology Life Quality Index to Week 16							
N Mean (SD)	170 -0.6 (6.4)	322 -11.2 (7.2)	N/A		248 -2.6 (6.9)	495 -11.3 (6.8)	N/A	
	Scalp-Specific Investigator's Global Assessment (ss-IGA) score of 0 or 1 with at least 2-grade improvement from baseline at Week 16 in subjects with baseline ss-IGA ≥2							
	21/145 (14%)	231/277 (83%)	N/A	<0.001	22/202 (11%)	329/408 (81%)	N/A	<0.001
	Change from baseline Psoriasis Symptom and Sign Diary Score to Week 16							
N Mean (SD)	129 -3.0 (19.6)	249 -41.9 (24.6)	N/A		198 -8.3 (23.7)	411 -40.1 (26.5)	N/A	

N_{US} = Data from United States + Canada which used or compared to US-licensed adalimumab, N/A = not applicable, SD = standard deviation

5 Risk Assessment & Safe-Use Conditions

Safety data from studies VOYAGE 1 and VOYAGE 2 was pooled and serves as the primary safety analysis. Supportive safety data was taken from study NAVIGATE and PSO2001. A total of 1748 subjects with moderate-severe plaque psoriasis received guselkumab at the labeled dosage in clinical trials. In the 16-week placebo controlled period of the pooled clinical trials, adverse events occurred in 49% of subjects in the guselkumab group compared with 47% of subjects in the placebo group and 49% of subjects in the adalimumab group. Common AEs that occurred at a rate of at least 1% and at a higher rate in the guselkumab group than in the placebo group during the 16-week placebo-controlled period include upper respiratory infections (URI), headache, injection site reactions, arthralgia, (b) (4), elevated liver enzymes, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. In the 16-week placebo controlled period, elevated liver enzymes occurred more frequently in the guselkumab group (2.6%) than in the placebo group (1.9%). Of the 21 subjects with elevated LFTs in the guselkumab group, all were mild to moderate in severity and did not lead to treatment discontinuation. These identified adverse reactions will be conveyed in Section 6 of the Prescribing Information.

Through Week 48, no new adverse drug reactions were identified with guselkumab use and the frequency of the adverse drug reactions was similar to the safety profile observed in the 16-week treatment period.

Safety data from NAVIGATE focused on randomized subjects receiving guselkumab or ustekinumab from Week 16-40. This safety evaluation is confounded somewhat because all subjects received ustekinumab at Week 0 and 4. Safety results from NAVIGATE from Week 16-40 were similar to VOYAGE 1 and VOYAGE 2. Additionally, further cardiovascular analyses were completed due to the epidemiologic associations between psoriasis and cardiovascular (CV) events.

5.1 DEATHS

Five deaths were reported across the core psoriasis studies in the development program. Two subjects received guselkumab, one subject received adalimumab, one subject received ustekinumab, and one subject received ustekinumab and guselkumab. Of the deaths in subjects receiving guselkumab, in study PSO2001 (Phase 2), a 55 year old obese white male with a history of smoking and alcohol use developed hyperlipidemia while receiving guselkumab. He experienced a myocardial infarction (MI) on Day 194 and died on Day 208 after progressive deterioration of his status.

After the database lock, the Sponsor became aware of two additional deaths reported in ongoing phase 3 studies. In study VOYAGE 1, a 43-year-old male with a history of depression treated with citalopram died approximately one week after his Week 68 visit after treatment with guselkumab as a result of "sudden death/probable suicide." DDDP requested a consultative review from the Division of Psychiatry Products (DPP) to evaluate psychiatric adverse events and provide recommendations for the labeling of psychiatric adverse reactions for this product. The consultant reviewer from DPP noted that the rates of psychiatric morbidity, including depression and suicidal behavior are higher among patients with psoriasis relative to the general population and, in previous psoriasis trials, suicidal ideation and behavior (SIB) events were increased with brodalumab while symptoms of depression were reduced by etanercept. The DPP consultant review concluded that the data does not suggest an increased risk of SIB or psychiatric adverse events with guselkumab in patients with plaque psoriasis that would justify prominent labeling of SIB or other psychiatric adverse events.[6]

In study NAVIGATE, a 67-year-old male with a six-week history of left neck mass with palpable lymph nodes was diagnosed at Week 60, his final visit, with a squamous cell carcinoma after treatment with guselkumab. He died nine months after diagnosis.

The Sponsor noted that these causes of death are consistent with those commonly observed in a population with moderate to severe psoriasis. The clinical reviewer concurs that treatment with guselkumab did not appear to increase risk of mortality.

5.2 SERIOUS ADVERSE EVENTS (SAES)

The most common SAEs in guselkumab treated subjects were infection-related events and were generally singular events with no identifiable pattern. Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a safety signal.

5.3 INFECTIONS

Infection is a risk for guselkumab based on its immune-modulating mechanism of action. In the 16-week placebo-controlled period, infections occurred more frequently in subjects who received guselkumab compared to those who received placebo (23% vs 21%). Most cases of infections were upper respiratory infections, gastroenteritis, tinea, and herpes simplex (HSV) infections and were mild to moderate in severity and did not lead to discontinuation of guselkumab.

In the pooled Phase 3 trials through Week 16, the number of serious infections was similar in the guselkumab group (1 erysipelas [0.1%]) compared with the placebo group (1 chronic cholecystitis [0.2%]) and less than the adalimumab group (2 cellulitis [1.02%]). Additional reports of serious infections

through Week 28 included two subjects in the guselkumab group (bronchitis and soft tissue infection) and two subjects in the placebo to guselkumab crossover group (anal abscess and wound infection). Through Week 48, the event rate for serious infection was 1.17/100 subject years of follow up in the guselkumab group compared with 0.78/100 subject years of follow up in the placebo group and 2.12/100 subject years of follow up in the adalimumab group. The majority of serious infections were single events (except cellulitis). There were no reports of active TB or opportunistic infection in any guselkumab treated subject through week 48 in studies VOYAGE 1 and VOYAGE 2.

5.4 MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Given the epidemiologic associations between psoriasis and cardiovascular (CV) events, and the potential association between anti-cytokine therapies used in the treatment of moderate-to-severe psoriasis and CV events, the Sponsor conducted additional analyses on CV events. Cardiovascular event data was analyzed from Phase 2 (PSO2001) and Phase 3 trials (VOYAGE 1, VOYAGE 2, and NAVIGATE). MACE was defined as a composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. "Other CV events" included hospitalization for unstable angina (HUA), transient ischemic attack (TIA), venous thromboembolic event (VTE), peripheral arterial thrombotic event, coronary revascularization (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery), heart failure (HF), arrhythmia requiring intervention, CV-related syncope, and severe/accelerated hypertension leading to hospitalization.

DDDP requested input from the Division of Cardiovascular and Renal Products (DCRP) on the cardiovascular findings and proposed labeling.[7] The cardiology reviewer noted 15 MACE events in studies PSO2001, VOYAGE 1, VOYAGE 2, and NAVIGATE combined; of those, 10 were in subjects exposed to guselkumab. In the four studies combined, the annualized MACE rate was 0.84/100 subject-years for guselkumab, 0.63/100 subject years for adalimumab, and 5.08/100 subject years for the ustekinumab treatment group. Eight out of a total of 12 MIs occurred in subjects receiving guselkumab. The imbalance in MIs was driven largely by findings in a single trial (VOYAGE 2) where 4 subjects in the guselkumab arm experienced MIs compared to 1 subject receiving adalimumab. The cardiology reviewer states that this difference may be a true treatment difference, the effect of other differences in these subgroups, or a statistical anomaly. Fifteen "other CV events" occurred in studies PSO2001, VOYAGE 1, VOYAGE 2, and NAVIGATE combined including 7 arrhythmias requiring intervention (2 in guselkumab treated subjects), 4 HF events (1 in a guselkumab treated subject), 2 HUAs (both in guselkumab treated subjects), 1 VTE, and 1 PCI.

The Sponsor concluded that the event rate for adjudicated MACE in the guselkumab group was low and comparable to that for the adalimumab group in the pooled safety analysis set for all three time periods. The incidence of MACE through one year of treatment with guselkumab was low, comparable with adalimumab, and not suggestive of any association with guselkumab treatment. The cardiology reviewer concluded that subjects experiencing MACE events generally had risk factors for CV disease. Based on the available data, at this time evidence of a clinically meaningful imbalance in MACE or "other CV events" with guselkumab was not observed. DCRP does not recommend that MACE or hypertension be included in the labeling for guselkumab.

6 Expected Postmarket Use

Guselkumab is likely to be prescribed by dermatologists. Guselkumab may be administered by a healthcare professional or a patient may self-inject after proper training in subcutaneous injection technique. Healthcare providers who are likely to prescribe guselkumab should be familiar with treatment regimens that include immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23. Other medications used to treat psoriasis, including infliximab, adalimumab, etanercept, and ustekinumab, which had REMS to mitigate the risks of infections and malignancies, have been released. Their REMS assessments showed that healthcare professionals understood the key messages regarding immunomodulating agents and risk of infection. Since the likely prescribers of guselkumab and these products are the same, it is likely that prescribers are aware and knowledgeable about the risks of immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23.

7 Risk Management Activities Proposed by the Sponsor

The Sponsor did not propose any risk management activities for guselkumab beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of guselkumab based on the efficacy and safety information currently available.

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has substantial impact on patients' lives. The benefits of treatment with guselkumab were demonstrated by meeting the primary endpoints of the clinical trials. Based on these results, guselkumab was found to be highly efficacious with an acceptable safety profile for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Safety concerns associated with the use of guselkumab for moderate-to-severe psoriasis are well documented. The safety profile demonstrated for guselkumab is consistent with the known safety profiles of other systemic agents used for the treatment of moderate-to-severe psoriasis and includes the risk of immunosuppression with the associated risks of serious infections and reactivation of tuberculosis. Healthcare providers who are likely to prescribe guselkumab should be familiar with treatment regimens that include immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23. Labeling will include infections, pre-treatment evaluation of tuberculosis, and avoidance of live immunizations in the Warnings and Precautions section.

A theoretical risk of malignancy exists due to immunosuppressive effects, and is hypothesized to be a potential risk for all psoriasis biologics. The Division of Epidemiology I (DEPI-I)[8] has determined that active risk identification and analysis (ARIA) is sufficient for evaluation of short-term lymphoma and

insufficient for long-term malignancy. A long-term prospective observational study will be a post-marketing requirement (PMR) to assess long-term malignancy risk and other secondary outcomes such as serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events among guselkumab users. Similar biologics, such as Taltz (ixekizumab), Siliq (brodalumab), and Cosentyx (secukinumab), were issued PMRs to examine the risk of long-term malignancy and other secondary outcomes.

Additionally, other medications used to treat psoriasis, including infliximab, adalimumab, etanercept, and ustekinumab, which had REMS programs to mitigate the risks of infections and malignancies, have been released. Their REMS assessments showed that healthcare professionals understood the key messages regarding immunomodulating agents and risk of infection. Since the likely prescribers of guselkumab and these products are the same, it is likely that prescribers are aware and knowledgeable about the risks of immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23. Therefore, based on the data currently available, DRISK and DDDP agree that a REMS is not necessary to ensure the benefits outweigh the risks of guselkumab.

9 Conclusion & Recommendations

Based on the available data, it is this reviewer's opinion that a REMS is not necessary to ensure the benefits outweigh the risks. Guselkumab has proven to reduce the severity of symptoms in patients with moderate-to-severe plaque psoriasis. Based on the known safety profile for similar medications and the risks associated with guselkumab from the clinical trials, the benefit-risk profile is acceptable and the risks will be communicated through labeling. In general, healthcare providers who treat psoriasis should be familiar with the risks of serious infection.

Should DDDP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:

1. JRD. Proposed Prescribing Information for guselkumab, November 16, 2016.
2. JRD. Clinical Overview for guselkumab, November 16, 2016.
3. JRD. Summary of Clinical Safety for guselkumab, November 16, 2016.
4. McCord M, Clark K. DDDP. Memorandum for guselkumab BLA 761061, June 13, 2017.

11 Appendices

11.1 FDA Approved Drugs for Treatment of Plaque Psoriasis

Drug (class)	Route	REMS/Boxed Warning/MG
Acitretin (retinoid)	Oral	RiskMAP, Boxed Warning (Pregnancy/teratogen, hepatotoxicity), MG
Adalimumab (TNF blocker)	Injectable	REMS Removed, Boxed Warning (Serious infections, Malignancy), MG
Apremilast (PDE4 inhibitor)	Oral	None
Brodalumab (IL-17A receptor antagonist)	Injectable	REMS w/ETASU (SIB), Boxed Warning, MG
Calcipotriene (Vit D derivative)	Topical	None
Calcipotriene/betamethasone dipropionate (Vit D derivative + corticosteroid)	Topical	None
Calcitriol (Vit D analog)	Topical	None
Cyclosporine (immunosuppressant)	Oral	Boxed Warning (infections, malignancy (skin), brands are not bioequivalent, hypertension, nephrotoxicity)
Desoximetasone (corticosteroid)	Oral	None
Dexamethasone sodium phosphate (corticosteroid)	Injectable	None
Etanercept (TNF blocker)	Injectable	REMS Removed, Boxed Warning (Serious infections, malignancy), MG
Infliximab (TNF blocker)	Injectable	REMS Removed, Boxed Warning (Serious infections, malignancy), MG
Ixekizumab (IL-17A antagonist)	Injectable	MG
Methylprednisolone (glucocorticoid)	Oral	None
Secukinumab (IL-17A antagonist)	Injectable	None
Tazarotene (retinoid)	Topical	None
Triamcinolone hexacetonide (glucocorticoid)	Injectable	None
Ustekinumab (IL-12 and IL-23 antagonist)	Injectable	REMS Removed, MG

11.2 References

[1] Usatine, Richard P, et al. "Chapter 152. Psoriasis." The Color Atlas of Family Medicine, 2e. Eds. Richard P. Usatine, et al. New York, NY: McGraw-Hill, 2013. N. pag. AccessMedicine. Web. 6 Oct. 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=685&Sectionid=45361214

[2] Liedtka J. DDDP. Clinical Review for Ixekizumab, BLA 1255521, dated November 20, 2015

[3] Cvetkovick, T. DRISK Review of 3-year REMS Assessment Report for Stelara, dated November 30, 2012

[4] Cvetkovick, T. DRISK Review of 7-year REMS Assessment Report for Stelara, dated December 22, 2016

[5] Choudhry, Y. Clinical Outcome Assessment Consult Review, dated April 8, 2017

[6] Umhau, K. Division of Psychiatry Products. Consultative review and evaluation of clinical data consult #11629, dated April 10, 2017.

[7] Hicks, Karen. Division of Cardiovascular and Renal Products, Cardiology Consult for Guselkumab, dated April 14, 2017

[8] Leishear White, K. Division of Epidemiology I. Active Risk and Identification Analysis (ARIA) Sufficiency Memo, Dated April 13, 2017.

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/s/

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06/27/2017

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06/28/2017