PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Bimzelx

This is a summary of the risk management plan (RMP) for Bimzelx. The RMP details important risks of Bimzelx, how these risks can be minimized, and how more information will be obtained about Bimzelx's risks and uncertainties (missing information).

Bimzelx's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Bimzelx should be used.

This summary of the RMP for Bimzelx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Bimzelx's RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Bimzelx is authorised for:

Plaque psoriasis: Bimzelx is indicated for treatment of adults with moderate to severe plaque psoriasis (PSO) who are candidates for systemic therapy (see SmPC for the full indication).

Psoriatic arthritis: Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs) (see SmPC for the full indication).

Axial spondyloarthritis:

- Non-radiographic axial spondyloarthritis (nr-axSpA): Bimzelx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).
- Ankylosing spondylitis (AS, radiographic axial spondyloarthritis): Bimzelx is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy (see SmPC for the full indication).

It contains bimekizumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Bimzelx’s benefits can be found in Bimzelx’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/bimzelx.

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

Important risks of Bimzelx, together with measures to minimize such risks and the proposed studies for learning more about Bimzelx's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Bimzelx is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing information

Important risks of Bimzelx are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bimzelx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 2–1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Serious infections
	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
Important potential risks	Serious hypersensitivity reactions
	Major adverse cardiovascular events
	Malignancy
Missing information	Use during pregnancy and lactation
	Long-term safety data

2.2 Summary of important risks

Table 2–2: Summary of important identified risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Serious infections are considered as an important identified risk as a class effect for IL-17 inhibitors.
Risk factors and risk groups	PSO: Increasing age, diabetes mellitus, smoking, significant infection history, and PSO treatment were each associated with an increased risk (Kalb et al, 2015). Treatment with biologics or small molecules may increase risk of serious infection in PSO patients, with variability in the mechanism of action (Siegel and Winthrop, 2019). PsA: Increasing age, prednisone use, PGA scores of 4 or 5 at the time closest to the reported event, history of infection, diabetes, chronic pulmonary comorbidity, and total duration of bDMARD use can potentially contribute to the risk of development of serious infections in PsA patients (Celkys et al, 2020, Ritchlin et al, 2019). axSpA: Annual average number of csDMARD prescriptions and time to first biological drug prescription are significantly associated with increased risk of hospitalization for infections in patients with AS (Quartuccio et al, 2019). The use of biologics among patients with AS and nr-axSpA are not significantly associated with an increased risk of serious infection (Wang et al, 2018b).
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, and AS0014 See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	
Evidence for linking the risk to the medicine	This risk is based on safety evaluation performed including pharmacoepidemiological background incidence and prevalence rates of IBD, comparison of data from other IL-17 inhibitors, and review of bimekizumab clinical data.

Table 2–2: Summary of important identified risks

Risk factors and risk groups	PSO: Risk of IBD in PSO patients increases with severity of disease and systemic medication usage. Cancer, obesity, and cardiovascular disease may also be risk factors of IBD in PSO patients (Lee et al, 2019; Radtke et al, 2017; Takeshita et al, 2017; Vlachos et al, 2016; Molodecky et al, 2012; Loftus Jr 2004). PsA: Risk of IBD in PsA increases with environmental risk factors such as smoking, infections, high doses of NSAIDs and genetic predisposition (Schreiber et al, 2019, Charlton et al, 2018). Previous failure of a TNF antagonist has also been associated with exacerbations and less disease control (Schreiber et al, 2019). axSpA: Risk of IBD in axSpA increases with environmental risk factors such as smoking, infections, genetic predisposition, previous failure of a TNF antagonist and high doses of NSAIDs (Schreiber et al, 2019; Fragoulis 2019). People in the older age group (≥65 years) and those with comorbidity of cancer also have a higher risk for IBD (Wang et al, 2020).
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, and AS0014 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; bDMARD=biologic disease-modifying antirheumatic drug; csDMARD=conventional synthetic disease-modifying antirheumatic drug; IBD=inflammatory bowel disease; IL=interleukin; NSAID=non-steroidal anti-inflammatory drug; nr-axSpA=non-radiographic axial spondyloarthritis; PGA=physician global assessment; PSO=psoriasis; TNF=tumor necrosis factor

Table 2–3: Summary of important potential risks

Important potential risk: Serious hypersensitivity reactions	
Evidence for linking the risk to the medicine	All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactic/anaphylactoid events. Data to evaluate safety concerns derive from clinical studies.
Risk factors and risk groups	Risk groups include patients who have hypersensitivity to the active substance or to any of the excipients.
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, and AS0014

Table 2–3: Summary of important potential risks

	See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Important potential risk: MACE	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies, comparison of data from other IL-17 inhibitors, and pharmacoepidemiological background incidence and prevalence rates.
Risk factors and risk groups	PSO: The increased cardiovascular risk in PSO patients is partly due to the association with factors that are known predictors of cardiovascular risk including hyperlipidemia, obesity, hypertension, and diabetes. In addition, PSO patients have an increased risk of vascular inflammation and MACE (defined as myocardial infarction, stroke and cardiovascular related death) beyond that attributable to known cardiovascular risk factors (Egeberg et al, 2017; Gelfand et al 2006). Observational studies have shown that if systemic inflammation is driving CVD risk then systemic treatment with methotrexate and biologic drugs may reduce elevated risk of MACE (Jindal and Jindal, 2018). Some clinical trials of IL-12/23 inhibitors have reported elevated risk of MACE; however, a recent review across 38 RCTs found no statistically elevated risk (Rungapiromnan et al, 2017; Parisi et al, 2015). PsA: In PsA patients, the risk of developing CV events is driven by traditional CV risk factors; however, the level of disease activity and the extent of systemic inflammatory factors and chronic recurring inflammation are predictors of CV events (Zheng et al, 2022, Eder et al, 2016). Alongside traditional CV risk factors, such as diabetes, dyslipidemia, and smoking, markers of PsA disease activity, including polyarthritis, dactylitis, extensive skin PSO, and elevated inflammatory markers, have been associated with clinical CV events (Karmacharya et al, 2021c, Ogdie et al, 2015). axSpA: Inflammation, disease activity or its severity measurements are well-recognized factors for accelerated atherosclerosis in axSpA, along with traditional CV risk factors such as smoking, hypertension, obesity, diabetes, and dyslipidemia (Toussirot et al, 2021).
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, and AS0014 See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies, comparison of data from other IL-17 inhibitors, and pharmacoepidemiological background incidence and prevalence rates.
Risk factors and risk groups	PSO: Several mechanisms may contribute to the increased risk of cancer among patients with PSO including chronic inflammation, impaired

Table 2–3: Summary of important potential risks

	immunosurveillance associated with the disease itself. Other factors, such as treatment with certain pharmacologic agents or behavioral factors including smoking and alcohol consumption also may contribute to risk independently. A large meta-analysis showed that risk factors of cancer in PSO patients included alcohol and cigarette use, phototherapy, and disease severity (Pouplard et al, 2013). Two retrospective cohort studies examined severity of PSO disease and/or treatment in relation to cancer incidence (Kimball et al, 2015; Lee et al, 2012). These studies found a trend in the incidence of all cancers, lymphoma, melanoma, and NMSC associated with increased PSO disease severity defined by treatment. PsA: The increased risk of cancers in PsA could be driven by the chronic inflammatory nature of the disease itself and the requirement for long-term therapy with immunosuppressive agents and/or phototherapy. An increased risk of cancer can also be attributed to more severe form of PsA which requires more long-term use and high-cumulative dose of immunosuppressants. Although data on the risk of cancer for the different therapeutic domains in PsA are variable, patients treated with conventional synthetic disease modifying antirheumatic drugs are reported to present with increased cancer risk, but not those treated with biological therapies (Vaengebjerg et al, 2020; Woo et al, 2020; Fagerli et al, 2019; Luo et al 2019; Costa et al, 2016; Hagberg et al, 2016). axSpA: Chronic inflammatory activity in patients with AS can drive the risk of developing malignancies in axSpA. Evidence suggests that Asian populations, but not American or European populations, have a higher risk of malignancy (Deng et al, 2016). A meta-analysis has indicated no overall elevated risk of malignancy among SpA patients (including axSpA and peripheral SpA) treated with biologics (Kwan et al, 2020).
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, and AS0014 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; COPD=chronic obstructive pulmonary disease; COX=cyclooxygenase; CV=cardiovascular; CVD=cardiovascular disease; IL=interleukin; MACE=major adverse cardiovascular event; NMSC=nonmelanoma skin cancer; PsA=psoriatic arthritis; PSO=psoriasis; RCT=randomized clinical trial; SpA=spondyloarthritis

Table 2–4: Summary of missing information

Missing information: Use during pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures: Product labeling

Table 2–4: Summary of missing information

Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0036 (Bimekizumab pregnancy exposure and outcomes registry) PS0037 (An observational cohort study to evaluate bimekizumab exposure during pregnancy) See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Review of safety data from studies PS0014, PS0015, PA0012, and AS0014 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bimzelx.

2.3.2 Other studies in post-authorisation development plan

Additional pharmacovigilance activities include the following studies:

2.3.2.1 PS0038: Bimekizumab real-world outcomes study

- **Study short name:** Bimekizumab real-world outcomes study

  Purpose of the study: The primary objective of this observational cohort study will be to evaluate any potential increase in the risk of safety outcomes of interest in bimekizumab exposed PSO, PsA, and axSpA patients compared to PSO, PsA, and axSpA patients exposed to other biologics indicated for moderate-to-severe PSO, PsA, and axSpA except for any other anti-interleukin(IL)-17 biologics (eg, anti-tumor necrosis factor[TNF], anti-IL-23) in the real-world setting.

  The safety outcomes of interest will include but are not limited to major adverse cardiovascular events, malignancy, serious infections, inflammatory bowel disease, and serious hypersensitivity reactions.

2.3.2.2 PS0036: Bimekizumab pregnancy exposure and outcomes registry

- **Study short name:** Bimekizumab pregnancy exposure and outcomes registry

  Purpose of the study: The objective of this study is to assess maternal, fetal, and infant outcomes among women who become pregnant while exposed to bimekizumab relative to the outcomes in 2 frequency matched comparator populations. The primary analysis will be a comparison of the birth prevalence of major structural defects in live born infants between

the bimekizumab-exposed cohort and the disease comparison cohort. Additional outcome variables will be to evaluate the potential effect of bimekizumab exposure on other adverse pregnancy outcomes including, but not limited, to spontaneous abortion, elective termination, stillbirth, preterm delivery, and infant outcomes including small for gestational age, pattern of 3 or more minor structural defects, postnatal growth (to 1 year of age), developmental concerns (at approximately 1 year of age), and serious infections (up to 1 year of age).

2.3.2.3 PS0037: Observational cohort study to evaluate bimekizumab exposure during pregnancy

- **Study short name:** Observational cohort study to evaluate bimekizumab exposure during pregnancy

  Purpose of the study: The primary objective is to assess adverse pregnancy and infant outcomes, more specifically major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, preterm birth and infant infections, in women exposed to bimekizumab during pregnancy compared to women exposed to other biologics indicated for moderate-to-severe PSO, PsA, axSpA, and any condition for which bimekizumab has an approved indication except for any other anti-IL-17 biologics (eg, anti-TNF, and-IL-23) during pregnancy using a cohort study design with data from a large electronic health database.

2.3.2.4 PS0014

- **Study short name:** A multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO (PS0014).

  Purpose of the study: To assess the long-term safety and tolerability of bimekizumab administered sc in adult study participants with moderate to severe chronic plaque PSO. This study will include 2 periods, a Treatment Period (144 weeks) and a SFU period (20 weeks after the final dose). A second open-label extension (OLE) Period was added, during which eligible study participants in Canada and the US are invited to continue or reinitiate bimekizumab treatment for an additional 40 weeks and are followed in a second SFU Period of 20 weeks after the final dose of investigational medicinal product (IMP), as appropriate. This will allow continuous access to bimekizumab for study participants in Canada and the US.

2.3.2.5 PS0015

- **Study short name:** A multicenter, randomized, double-blind, active comparator-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO (PS0015).

  Purpose of the study: The open label extension period will allow collection of long-term efficacy and safety data from eligible study participants on open-label bimekizumab for an additional 96 weeks (after 48 weeks of initial treatment). An OLE2 Period was added, during which eligible study participants in Canada and the US are invited to continue or reinitiate bimekizumab treatment for an additional 40 weeks and are followed in a second SFU Period of 20 weeks after the final dose of IMP, as appropriate. It will allow continuous access to bimekizumab for study participants in Canada and the US.

2.3.2.6 PA0012

- **Study short name**: A multicenter, open label extension study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with active PsA.

  Purpose of the study: The open label extension period will allow collection of long-term safety and tolerability data of bimekizumab over a period of up to 140 weeks in adult participants with PsA who completed the feeder Phase 3 studies. An OLE 2 Period was added, during which eligible participants in the US, France, Germany, and Japan are invited to continue or reinitiate bimekizumab treatment for an additional 52 weeks and are followed in a SFU Period of 20 weeks after the final dose of IMP (SFU Period), as appropriate.

2.3.2.7 AS0014

- **Study short name:** A multicenter, open label extension study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with axSpA (radiographic and non-radiographic).
- **Purpose of the study:** The open label extension period will allow collection of long-term safety and tolerability data of bimekizumab over a period of up to 112 weeks in adult participants with axSpA who completed the feeder Phase 3 studies. An OLE 2 Period was added, during which eligible study participants in Japan, France, Germany, and US are invited to continue bimekizumab treatment for an additional 52 weeks and are followed in a SFU Period of 20 weeks after the final dose of IMP (SFU Period), as appropriate.