EU RISK MANAGEMENT PLAN
FOR
ZYNYZ (RETIFANLIMAB)

RMP version to be assessed as part of this application: v0.4

Data lock point for this RMP	20 MAY 2022	Version number	V 0.4
Date of final sign off	09 FEB 2024		

Rationale for submitting an updated RMP:

Updates to the RMP are based on the CHMP and PRAC Day 195 Joint Assessment Report dated 7 FEB 2024.

Summary of significant changes in this RMP:

Part	Major changes in v0.3 compared to v0.4
Part II Modules: SIV.1; SVII.3.1	Immune-related adverse event was updated to immune-mediated adverse event when summarizing the important risks and populations not studied in clinical trials.
Part V.1	Immune-related adverse event was updated to immune-mediated adverse event when referencing the SmPC and PL.
Part VI II.B	Immune-related adverse event was updated to immune-mediated adverse event when summarizing the important risks.

Other RMP versions under evaluation:

No RMP versions are currently under evaluation

QPPV name: Cláudia Serafim

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BALT	bronchus associated lymphoid tissue
CNS	central nervous system
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
ESMO	European Society of Medical Oncology
EU	European Union
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
HIV	Human immunodeficiency virus
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
IgG	immunoglobulin G
IHC	immunohistochemistry
Immune-mediated AE	Immune-mediated adverse event
IRR	infusion-realted reaction
IV	intravenous
kg	kilogram
m^2	meters squared
mAb	monoclonal antibody

Abbreviation	Definition
MAH	Marketing Authorisation Holder
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
mg	milligram
mL	milliliter
µg	microgram
NCCN	National Comprehensive Cancer Network
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OS	overall survival
PD-1	programmed death receptor-1
PD-L1/2	programmed death receptor-ligand 1/2
PL	package leaflet
PSUR	periodic safety update report
PT	preferred term
Q4W	every 4 weeks
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
ULN	upper limit of normal
UV	ultraviolet

PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	retifanlimab
Pharmacotherapeutic group(s) (ATC Code)	Pending - L01XC*AA*
Marketing Authorisation Applicant	Incyte Biosciences Distribution B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zynyz
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Biological - IgG4κ Monoclonal antibody
	Summary of mode of action: Designed to target PD-1-expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2
	Important information about its composition: Biological product produced in Chinese Hamster Ovary cells
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current: Monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma not amenable to curative surgery or radiation therapy
	Proposed (if applicable): N/A
Dosage in the EEA	Current: 500 mg administered IV over 30 minutes every 4 weeks
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current: Concentrate for solution for infusion, 500 mg/20 mL vial (25mg/mL)
	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma not amenable to curative surgery or radiation therapy.

Incidence & Prevalence:

Merkel cell carcinoma (MCC) is an ultra-rare, aggressive, life-threatening, cutaneous malignancy with a poor outcome when advanced. The approximate annual incidence is 0.13 per 100,000 persons in Europe (van der Zwan et al 2013). The annual incidence is increasing in multiple countries at a faster rate than other solid tumors (Fondain et al 2018, Girschik et al 2011, Reichgelt and Visser 2011, Robertson et al 2015, Youlden et al 2014, Zaar et al 2016). The annual incidence of MCC worldwide varies between 0.13 and 1.6 per 100,000 persons (Schadendorf et al 2017). It is unclear if the incidence range reflects different environmental or genetic factors or earlier detection of the disease (Girschik et al 2011, Hodgson 2005, Mills et al 2006, Youlden et al 2014).

RARECARENet, a Europe-wide surveillance resource for rare cancer treatment and statistics, estimates an age-adjusted incidence of 0.147 per 100,000 persons for MCC over time in Europe from 2003 to 2007, which translates to 1,614 new cases of MCC during that period (RARECARENet 2022).

GLOBOCAN 2020, a worldwide cancer surveillance database, estimates in Europe, that though there are 356,180 incident cases of non-melanoma skin cancer, less than 1% of the non-melanoma skin cancer cases are MCC (Katalinic et al 2003, Samarasinghe et al 2012, Cives et al 2020, Ciążyńska et al 2021, Gauci et al 2022, EADV 2019, Orphanet 2022). MCC is rare in Europe, with an estimated annual incidence of 0.078 per 10,000 persons.

RARECARENet estimates a complete prevalence of 6,513 MCC cases in Europe on 01 January 2008, for an estimated prevalence of 0.013 per 100,000 persons (RARECARENet2022).

According to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation" (COMP/436/01) and assuming a stable incidence and disease duration, prevalence (P) can be calculated as P = I x D, where: I = incidence and D = mean disease duration. An indirect calculation of prevalence using estimates, derived from GLOBOCAN database, that about 3,500 new cases of MCC are diagnosed annually in Europe, 5-year overall survival rate ranges from 48% to 64% for MCC (Gauci et al 2022, Paulson et al 2018), and Eurostat estimates a population of 446.8 million for the EU-27 shows MCC has a estimated prevalence of 0.39 per 10,000 persons in the EU-27.

Demographics of the population in the proposed indication and risk factors for the disease:

The principal environmental risks for MCC are ultraviolet (UV) radiation and Merkel cell polyomavirus (MCPyV) infection; as a result, elderly, fair-skinned individuals with a history of chronic sun exposure have the highest risk of developing MCC (Dellambra et al 2021, Gauci et al 2022, Harms et al 2016, Paulson et al 2018). Non-White patients represent 2.2% to 3.5% of cases, and approximately two-thirds of all MCC cases are diagnosed in males (Freeman et al

2019, Gauci et al 2022, Harms et al 2016, Paulson et al 2018, Yaghi et al 2022). Immunocompromised status (eg, due to other malignancies, HIV, or solid organ transplant) is also a recognized risk factor for MCC (Clarke et al 2015, Dellambra et al 2021, Engels et al 2002, Koljonen et al 2009, Paulson et al 2018, Yaghi et al 2022).

The main existing treatment options:

Historically, metastatic MCC has been treated with chemotherapy regimens similar to those used for small cell lung cancer. Initial therapy with platinum-based chemotherapy provides high response rates; however, these are of short duration (median DOR of approximately 3 months; Iyer et al 2016). No survival advantage has ever been demonstrated for chemotherapy (Cassler et al 2016, Gauci et al 2022, Hughes et al 2014, NCCN 2022, Voog et al 1999). Management of patients with recurrent, locally advanced, unresectable MCC is also challenging (Becker et al 2017). Similar to distant metastatic disease, patients with recurrent, unresectable MCC require systemic therapy to achieve disease control. Chemotherapy is both less effective in the salvage setting (Iyer et al 2016), and also associated with risk of severe toxicity and toxic death, particularly among older patients who, as noted, have the highest incidence of the disease (Gauci et al 2022, Voog et al 1999). As a consequence, chemotherapy is no longer considered a preferred treatment for metastatic MCC in consensus guidelines (Gauci et al 2022, NCCN 2022).

Immunotherapy has proved to be a major advance in the treatment of MCC and the PD-(L)1 inhibitor avelumab is now indicated as monotherapy for the treatment of adult patients with metastatic MCC based on the results of Study EMR100070-003 (JAVELIN Merkel-200) that enrolled participants with both chemotherapy-refractory (Part A) and chemotherapy-naïve (Part B) metastatic MCC (D'Angelo et al 2021a, D'Angelo et al 2021b). Retifanlimab is recently approved in the United States for treatment of metastatic or recurrent locally advanced MCC based on results of INCMGA 0012-201. Pembrolizumab and nivolumab have also been shown to have substantial activity in this disease (Nghiem et al 2021, Topalian et al 2017).

Natural history of the indicated condition in the population, including mortality and morbidity:

Presentation of MCC is usually with a nonspecific, erythematous lesion in sun-exposed areas. Lesions may grow and metastasize quickly; 26% to 36% of patients present with lymph node involvement, and 6% to 16% of patients present with distant metastatic disease (Agelli and Clegg 2003, Albores-Saavedra et al 2010, Harms et al 2016, Hodgson 2005, Lemos et al 2010, Sridharan et al 2016). MCC metastasizes first to lymph nodes and spread is typically to lung, adrenal glands, pancreas, liver, brain, and bones (Dellambra et al 2021). The 5-year survival rates are poor; 35% for those with nodal involvement and only 14% for metastatic disease (Harms et al 2016, Trinidad et al 2019).

Important co-morbidities:

Elderly (≥65 years old), fair-skinned individuals with a history of chronic sun exposure have the highest risk of developing MCC and approximately two-thirds of all MCC cases are diagnosed in males (Dellambra et al 2021,Freeman et al 2019, Gauci et al 2022, Harms et al 2016, Paulson et al 2018, Yaghi et al 2022). In a large-scale claims analysis the average age at diagnosis was 68.8 years, 60.3% were ≥65 years of age, and 60.3% were male. The mean Charlson/Deyo comorbidity index score was 2.14 (SD 2.26) with 42.3% of patients ≥65 years having a score ≥3. The most common comorbidities during follow-up were diabetes (27.8%),

chronic pulmonary disease (23.1%), cerebrovascular disease (19.2%), congestive heart failure (14.2%), and renal disease (14.0%) (Kearney et al 2018).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Nonclinical Toxicology

The nonclinical toxicology program for retifanlimab consisted of single-dose toxicity, repeat-dose toxicity, and tissue cross-reactivity studies and was designed in accordance with ICH S9 (2010) and ICH S6(R1) (2011). Retifanlimab was well tolerated in single-dose and repeat-dose (4-week [doses up to 150 mg/kg] and 13-week [up to 100 mg/kg]) toxicology studies. There were no preterm deaths or treatment-related toxicities. There were no changes in clinical signs, body weights, food consumption, physical examinations, ophthalmology, body temperature, blood pressure, heart rate, respiration rate, neurological examinations, electrocardiograms (ECGs), clinical chemistry, coagulation, gross pathology, or organ weights.

Single-Dose Toxicity:

Non-GLP Single Dose PK Study in Cynomolgus Monkeys

In this non-GLP study (T15-06-12), retifanlimab was compared to two other anti-PD-1 IgG4,κ mAbs: MK 3475 (also known as pembrolizumab [Keytruda®, Merck]) and AEX1197, an anti-PD-1 antibody constructed by MacroGenics based on the published sequence for nivolumab (Opdivo®, Bristol-Myers Squibb) hereafter referred to as the nivolumab replica. Each antibody was administered at 10 mg/kg by 1-hour IV infusion to 2 monkeys (1M, 1F) and animals were monitored for 65 days, at which time they were returned to the colony.

Administration of a single-dose of retifanlimab by IV infusion was well tolerated in cynomolgus monkeys at a dose level of 10 mg/kg. There were no changes in circulating immune cell subsets and no evidence of cytokine release. Binding profiles of retifanlimab to PD-1 on $CD4^+$ and $CD8^+$ T cells were similar to those exhibited by pembrolizumab, but more durable than those exhibited by nivolumab replica and correlated with serum concentration.

Repeat-Dose Toxicity:

3-Week Repeat Dose Non-GLP Toxicology Study in Cynomolgus Monkeys

Cynomolgus monkeys (1/sex/group) were administered retifanlimab by 1 hour IV infusion once weekly for 3 weeks at doses of 0 (vehicle), 1, or 100 mg/kg (T15-08-05; Non-GLP). Animals were euthanized 3 days (Day 18) or 7 days (Day 22) after the final dose.

All retifanlimab-treated animals survived until scheduled euthanasia. There were no retifanlimab-related changes in clinical signs, food consumption, body weights, body temperature, hematology, coagulation, clinical chemistry, immunophenotyping parameters, or gross necropsy findings.

Administration of retifanlimab by IV infusion once weekly for 3 weeks (Days 1, 8, and 15) was well tolerated in cynomolgus monkeys at levels of 1 and 100 mg/kg. A dose-dependent mild to moderate lymphohistiocytic cellular infiltrate of the splenic red pulp was observed at both 1 and 100 mg/kg retifanlimab.

4-Week GLP Study in Cynomolgus Monkeys With a 10-Week Recovery Period

Cynomolgus monkeys (5/sex/group) were treated with retifanlimab by weekly IV infusion over 1 hour at doses of (vehicle), 10, 40, or 150 mg/kg (GLP Study T19-01-03). Six animals (3/sex/group) were necropsied on Day 25, while the remaining animals (2/sex/group) were necropsied on Day 95.

All animals survived until scheduled necropsy on Days 25 or 95. There were no retifanlimab-related effects on clinical observations, body weights, ECGs, ophthalmology, serum chemistry parameters, urinalysis, gross pathology, or organ weights.

Administration of retifanlimab by IV infusion once weekly for 4 weeks was clinically well tolerated at levels up to 150 mg/kg. Effects observed were limited to transient decreases in circulating lymphocytes and minimal injection-site changes related to injection of a foreign protein. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg (sex combined mean Cmax of 3.94 mg/mL and AUC of 746 h•mg/mL).

A diffuse pattern of immune cell infiltration was observed histologically in treated animals that was considered of uncertain relationship to retifanlimab based on the lack of a dose-response and/or similar findings in control animals, although these findings are similar to the immune cell infiltration observed in repeat-dose studies with cynomolgus monkeys treated with the approved anti-PD-1 antibodies, pembrolizumab and nivolumab (Herzyk and Haggerty 2018, Wang et al 2014) and are consistent with the mechanism of action of anti-PD-1 antibodies – blocking signaling through the immunoinhibitory PD-1 – PD-L1/L2 pathway.

13-Week Repeat Dose GLP Toxicity Study

Cynomolgus monkeys (5/sex/group) were administered retifanlimab once weekly by IV infusion over 30 minutes at doses of 0, 5, 20, or 100 mg/kg for 13 weeks [GLP study T18-02-10]. All animals were necropsied on Day 88.

All animals survived until scheduled necropsy. There were no retifanlimab-related clinical observations, or body weight, ECG, ophthalmology, serum chemistry, urinalysis, gross pathology, organ weight, or histopathology changes.

Administration of retifanlimab by IV infusion once weekly for 13 weeks was well tolerated in cynomolgus monkeys at levels of 5, 20, or 100 mg/kg. Effects observed were limited to decreases in lymphocytes in males on Day 2 to and minimal-to-moderate increases in fibrinogen in all groups dosed with retifanlimab. There were no retifanlimab-related histopathology findings. Based on these results, the NOAEL was considered to be 100 mg/kg.

Tissue Cross-Reactivity

A Tissue Cross-Reactivity Study of retifanlimab in Normal Human Tissues

Biotinylated retifanlimab (T16-02-22) was applied to cryosections of normal human tissues (3 donors per tissue, where available) at two concentrations (2.5 and 0.25 µg/mL), followed by a two-step indirect IHC staining method.

Retifanlimab-stained lymphocytes were most often observed in germinal centers in lymphoid organs (lymph node, spleen, and tonsil), except thymus which was primarily in medulla, and submucosal lymphoid aggregates in several human tissues including colon, esophagus, small intestine, kidney, ureter, cervix, uterus and lung (BALT) as well as tissues where lymphocytes

were present including kidney and prostate. This staining was judged expected based on literature reports of PD-1 expressed on T cells in lymphocytes in follicles of lymphoid organs (Breitfield et al 2000, Kim et al 2001, Schaerli et al 2000, Yang et al 2015). No unexpected tissue staining was observed with retifanlimab.

Safety Pharmacology

Evaluation of safety pharmacology endpoints were included in toxicology and/or pharmacodynamic studies. Evaluations in the 4-week GLP toxicology study (T19-01-03) conducted in cynomolgus monkeys included neurological examinations (general attitude, behavior, motor function, cranial nerves, proprioception and postural reactions, and spinal nerves) and body temperature; evaluation of blood pressure, heart rate, ECGs, and respiration rate; as well as clinical observations and gross and histologic examination. No retifanlimab-related findings suggestive of adverse effects on the central nervous system (CNS), cardiovascular, or respiratory systems were noted at any dose level evaluated in the 4-week study (10-150 mg/kg). In addition, no adverse effects on the CNS, cardiovascular, or respiratory systems were observed in the 13-week study as assessed based on clinical observations, ECGs, gross and histologic examinations (T18-02-10).

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The clinical trial exposure includes data from participants enrolled in 5 clinical studies (INCMGA 0012-101; -104; -201; -202; -203) who received retifanlimab as monotherapy. Data from the monotherapy clinical studies were pooled as follows:

- MCC Population (n=107), which includes all participants with MCC who received at least 1 dose of retifanlimab monotherapy. All participants in the MCC Population were enrolled in study INCMGA 0012-201 and received 500mg Q4W
- All Cancer Population (N = 653), which includes all participants with solid tumors who received at least 1 dose of retifanlimab as monotherapy. Four hundred fifty two of these participants (including all participants with MCC) received retifanlimab 500mg Q4W (referred to as "All Cancer 500 mg Q4W Population").

Table Part II: Module SIII.1: Duration of Retifanlimab Exposure by Dose

Duration of exposure	MCC Population	All Cancer Population	
	500 mg Q4W (N=107)	500 mg Q4W (N=452)	All Doses (N=653)
0 to ≤ 1 m, n (%)	21 (19.6)	89 (19.7)	144 (22.1)
>1 to ≤ 3 m, n (%)	10 (9.3)	87 (19.2)	147 (22.5)
>3 to ≤ 6 m, n (%)	10 (9.3)	64 (14.2)	103 (15.8)
>6 to ≤ 9 m, n (%)	7 (6.5)	34 (7.5)	51 (7.8)
>9 to ≤ 12 m, n (%)	10 (9.3)	34 (7.5)	38 (5.8)
>12 to ≤ 15 m, n (%)	15 (14.0)	29 (6.4)	33 (5.1)

>15 to ≤ 18 m, n (%)	7 (6.5)	16 (3.5)	19 (2.9)
>18 to ≤ 21 m, n (%)	6 (5.6)	24 (5.3)	25 (3.8)
>21 to ≤ 24 m, n (%)	17 (15.9)	69 (15.3)	82 (12.6)
> 24 m, n (%)[a]	4 (3.7)	6 (1.3)	11 (1.7)
Total patient years	95.6	331.9	416.9

[a] The maximum duration of treatment in retifanlimab clinical trials is 24 months

Table Part II: Module SIII.2: Demographics and Baseline Characteristics

	MCC Population	All Cancer Population	
	500 mg Q4W (N=107)	500 mg Q4W (N=452)	All Doses (N=653)
Age (years)			
Mean	70.7	66.2	63.4
Min	38	36	18
Median	71.0	67.0	65.0
Max	90	94	94
Age (category) (n [%])			
< 65 years	27 (25.2)	188 (41.6)	319 (48.9)
≥ 65 years	80 (74.8)	264 (58.4)	334 (51.1)
< 75 years	67 (62.6)	347 (76.8)	534 (81.8)
≥ 75 years	40 (37.4)	105 (23.2)	119 (18.2)
< 85 years	98 (91.6)	430 (95.1)	629 (96.3)
≥ 85 years	9 (8.4)	22 (4.9)	24 (3.7)
Gender (n [%])			
Male	73 (68.2)	192 (42.5)	259 (39.7)
Female	34 (31.8)	260 (57.5)	394 (60.3)
Ethnicity (n [%])			
Hispanic or Latino	1 (0.9)	10 (2.2)	27 (4.1)
Not Hispanic or Latino	81 (75.7)	310 (68.6)	485 (74.3)
Unknown	25 (23.4)	132 (29.2)	141 (21.6)
ECOG (n [%])			
0	77 (72.0)	219 (48.5)	270 (41.3)
1	30 (28.0)	230 (50.9)	378 (57.9)
2	0 (0.0)	2 (0.4)	4 (0.6)

	MCC Population	All Cancer Population	
	500 mg Q4W (N=107)	500 mg Q4W (N=452)	All Doses (N=653)
Missing	0 (0.0)	1 (0.2)	1 (0.2)

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Pregnancy or breastfeeding

Reason for exclusion: There are no data available on the use of retifanlimab in pregnant women. Based on its mechanism of action and a literature-based reproductive toxicity assessment, retifanlimab may cause fetal harm and/or disrupt the maintenance of normal pregnancy when administered to pregnant women. As reported in the literature, PD-1 / PD-L1 signalling pathway plays a role in sustaining pregnancy by maintaining immunological tolerance and studies have shown that PD-1 receptor blockade results in early termination of pregnancy (Petroff et al 2003, Miko et al 2019). The increase of spontaneous abortion and/or resorption in animals with restricted PD-L1 expression (knock-out or anti-PD1 / PD-L1 monoclonal antibodies) has been shown in both mice and monkeys (Guleria et al 2005). Since PD-1-/-mice develop late onset autoimmune phenotypes (Okazaki and Honjo 2007, Miko et al 2019), fetal exposure to retifanlimab may alter the normal immune response or increase the risk of developing immune-mediated disorders. These animal species have similar maternal-fetal interface to that in humans.

There are no data on the presence of retifanlimab or its metabolites in human milk, the effects of retifanlimab on the breastfed child, or on milk production. Retifanlimab is an IgG4 and antibodies (including IgG4) are secreted in human milk; a risk to breast-feeding newborns and infants cannot be excluded.

Is it considered to be included as missing information?: No

Rationale: The highest risk group for developing MCC are elderly, fair-skinned individuals with a history of chronic sun exposure and approximately two-thirds of all MCC cases are diagnosed in males (Dellambra et al 2021, Freeman et al 2019, Gauci et al 2022, Harms et al 2016, Paulson et al 2018). Retifanlimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. No further evaluation of embryofetal development is planned based on the reproductive toxicology assessment indicating that effects of the drug on maintenance of pregnancy would be anticipated and further studies would likely not be informative. Section 4.6 of the SmPC indicates that women of childbearing potential should use effective contraception during treatment with retifanlimab and for at least 4 months after the last dose. Further, accidental exposure of pregnant partners through the insemination route is unlikely to result in fetal exposures of concern given the low concentrations in semen that have been described with other IgG antibodies and the limited vaginal absorption that is likely to occur (Sohn et al 2015).

< 18 years of age

Reason for exclusion: The objective of retifanlimab clinical development was to demonstrate the efficacy and safety of retifanlimab in the adult population with MCC. The highest risk group for developing MCC are elderly, fair-skinned individuals with a history of chronic sun exposure (Dellambra et al 2021, Gauci et al 2022, Harms et al 2016, Paulson et al 2018).

Is it considered to be included as missing information?: No

Rationale: The highest risk group for developing MCC are elderly, fair-skinned individuals with a history of chronic sun exposure (Dellambra et al 2021, Gauci et al 2022, Harms et al 2016, Paulson et al 2018). Incyte Bioscience Distribution B.V. has submitted a full waiver application for retifanlimab in accordance with Article 12 of Regulation (EC) No 1901/2006. A pediatric investigation plan product specific waiver for all paediatric populations was granted by the EMA on 25 FEB 2022 (EMEA-002798-PIP02-21). Therefore, there is no plan for future pharmacovigilance activities to further characterize retifanlimab in a pediatric population with MCC.

Severe renal impairement (calculated creatinine clearance < 30 mL/min)

Reason for exclusion: Participants with severe renal impairment were excluded from the clinical trials of retifanlimab to avoid confounding factors for safety and to reduce risk of further kidney injury.

Is it considered to be included as missing information?: No

Rationale: Renal immune-mediated adverse events in immune checkpoint inhibitors (ICIs), unlike typical nephrotoxic drugs, do not have a dose-dependent toxic effect on the renal tubule (Sise et al 2019). Studies have shown that acute kidney injury (AKI) after ICI therapy did not occur more commonly in patients with baseline estimated glomerular filtration rate (eGFR) <60 mL per min per 1.73m^2 (Seethapathy et al 2019). The decision to treat with retifanlimab is to be made by the healthcare professional (HCP) after consideration of the patient's medical history/present medical condition, including the consideration of renal function testing performed before treatment, and enter treatment if clinically appropriate. Algorithms for the management of renal events are well-established in published clinical practice guidelines (Haanen et al 2017). Patients presenting with severe renal impairment would follow established

recommendations for the surveillance and management of renal function disturbances. Sections 4.2, 4.4, 4.8 and 5.2 of the SmPC describes the risk and management of immune-mediated nephritis and the renal impaired population.

Moderate or severe hepatic impairment (ALT >2.5 x ULN OR 5 x ULN for participants with liver metastases; AST >2.5 x ULN OR 5 x ULN for participants with liver metastases; Bilirubin ≥ 1.5 x ULN)

Reason for exclusion: Hepatitis occurs in 1 to 6% of patients treated with anti-PD- (L)-1 antibodies with rates of Grade 3 or 4 toxicity of 1-3% (Grover et al 2018). Patients with baseline severe liver dysfunction and poor hepatic reserve would be at risk for worsening liver function leading to worse overall outcomes.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with retifanlimab is to be made by the HCP after consideration of the patient's medical history/present medical condition, including the consideration of hepatic investigations performed before treatment. Algorithms for the management of hepatic events are well-established in published clinical practice guidelines (Haanen et al 2017). Patients presenting with moderate or severe hepatic impairment would follow established recommendations for the clinical surveillance and management of hepatic disturbances and be treated if clinically appropriate. Sections 4.2, 4.4, 4.8 and 5.2 of the SmPC describes the risk and management of immune-mediated hepatitis and the population with hepatic impairment.

Clincally significant cardiovascular disease

Reason for exclusion: Participants with clinically significant cardiaciovascular disease were excluded from the clinical trials of retifanlimab to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: Patients with comorbid cardiovascular risk factors may be at a slightly higher risk of immune-rmediated cardiovascular events with PD-1 inhibitor exposure, however, the overall incidence rates of these events are low. The four most common cardiovascular events (myocarditis, supraventricular tachycardia, acute pericarditis and vasculitis) are reported at an incidence rate less than 1% in clinical trials (Escudier et al 2017). Despite the clinical significance of these immune-mediated adverse events, the early recognition and management of potential cardiovascular events is well-characterized in the SmPC, and in the oncologic practice guidelines available to prescribers.

Clincally significant pulmonary compromise

Reason for exclusion: Participants with clinically significant pulmonary compromise were excluded from the clinical trials of retifanlimab to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: Patients with prior lung disease, including patients with lung cancer, may be a higher risk of pneumonitis than the general advanced cancer population exposed to PD-1 inhibitors. (Nishino et al 2016). For example, a multivariable analysis in of all grade pneumonitis found an overall frequency of 2.7% for PD-(L)1 monotherapy; pneumonitis was more frequent in non-

small cell lung cancer (NSCLC) patients, with an odds ratio of 1.43 95% CI, 1.08-1.89. Despite the clinical significance of these immune-mediated adverse events, the early recognition and management of potential pulmonary events is well-characterized in the SmPC, and in the oncologic practice guidelines available to prescribers.

Autoimmune disease

Reason for exclusion: Autoimmune diseases represent a broad group of clinical disorders that result from abnormal functioning of the immune system. Participants with autoimmune disease have been routinely excluded from oncology clinical trials with immune-checkpoint inhibitors, to avoid confounding factors for safety and efficacy, given the primary mechanism of action of this class of drugs in the immune system.

Is it considered to be included as missing information?: No

Rationale: Current published retrospective analyses of ICIs, including PD-1 inhibitors, demonstrate that cancer patients with pre-existing autoimmune diseases experience generally similar occurrence rates of toxicity, grades of toxicity, and rates of treatment discontinuation as cancer patients without prior history of autoimmune disorders. (Tang et al 2021, Yeung et al 2021, Xie et al 2020, Abdel-Wahab 2018). The benefit-risk of treating patients with auto-immune disease with PD-1 inhibitors is a shared decision between physician and patient, supported by well-characterized information on PD-1 inhibitors toxicities presented in the SmPC, and in oncology clinical practice guidelines.

History of allogeneic bone marrow, stem-cell, or solid organ transplants

Reason for exclusion: Participants with with a history of allogeneic bone marrow, stem-cell, or solid organ transplants have been routinely excluded from oncology clinical trials with immune-checkpoint inhibitors, to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: It has been reported in literature that responses as well as transplant rejection have been seen in patients with advanced cancer and concurrent soid organ transplants receiving PD-1/PD-L1 inhibitors (Tio et al 2018). The benefit-risk of treating patients with advanced cancer and concurrent solid organ transplants with PD-1 inhibitors is a shared decision between physician and patient.

Immunocompromised patients, other than well-controlled HIV

Reason for exclusion: Immunocompromised participants been routinely excluded from oncology clinical trials with immune-checkpoint inhibitors, to avoid confounding factors for safety and efficacy, given the primary mechanism of action of this class of drugs in the immune system.

Is it considered to be included as missing information?: No

Rationale: Current published analyses of PD-1 inhibitors demonstrate that the safety, tolerability, and efficacy of PD-1 inhibitors in immunocompromised patients, is consistent with what has been observed in clinical trials that excluded these patients. (Tio et al 2018). The benefit-risk of treating immunocompromised patients with PD-1 inhibitors is a shared decision between physician and patient, supported by well-characterized information on PD-1 inhibitors toxicities presented in the SmPC, and in oncology clinical practice guidelines.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Incyte Corporation proposes that the size of the safety database and extent of exposure will be sufficient to characterize the risk/benefit profile associated with retifanlimab and adequate to evaluate the safety and adverse event management guidance in support of a marketing application in MCC patients with limited therapeutic options and a life threatening disease. However, the ability of the clinical development programme to detect certain types of adverse reactions such as adverse reactions with long latency, or those caused by prolonged or cumulative exposure may be limited.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

This section aims to present the size of the safety database in each of the populations that are under-represented.

Table Part II: Module SIV.3: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with moderate or severe hepatic impairment • Patients with moderate or severe renal impairment • Patients with clinically significant cardiovascular impairment • Patients with clinically significant pulmonary impairment • Patients with autoimmune disease • Patients with a history of allogeneic bone marrow, stem-cell, or solid organ transplant • Immunocompromised patients, other than well-controlled HIV • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Retifanlimab clinical trials have been conducted globally in a variety of ethnic groups (see Table Part II: Module SIII.2). The majority of participants in the retifanlimab clinical trials have not been Hispanic or Latino.

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the MCC clinical development program
Other • Paediatric patients • Elderly patients	Paediatric: Not included in the clinical development program Elderly: The All Cancer 500mg Q4W Population (n = 452) was composed of 264 participants (58.4%) who were ≥ 65 years of age and 105 participants (23.2%) who were ≥ 75 years of age (see Table Part II: Module SIII.2).

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Zynyz was approved on 22 MAR 2023 in the US and is indicated for the treatment of adult patients with metastatic or recurrent locally advanced MCC. Zynyz is currently not approved in any other country.

SV.1.1 Method Used to Calculate Exposure

The current prescribed dosing for Zynyz is 500 mg administered as an intravenous infusion over 30 minutes every 4 weeks. Zynyz injection is supplied in a carton containing one single-dose 20 mL vial of 500 mg/20 mL (25 mg/mL).

The yearly average dose for one patient is estimated to be 6,500 mg (500 mg x 13 doses) in one patient-year. Given the total sales data up to 15 AUG 2023 is 10,500 mg (21 doses (vials) ordered), the total number of cumulative patient years of treatment is approximately 1.62 patient years (10,500 / 6,500).

SV.1.2 Exposure

The worldwide exposure cumulatively since launce of Zynyz up to 15 AUG 2023 is approximately 1.62 patient years.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on the mechanism of action and lack of psychopharmacologic effects retifanlimab has no addictive potential such as dependence and tolerance, thus the potential for misuse for illegal purposes is negligible. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged which would suggest a potential for abuse or dependence with retifanlimab.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

An evaluation of the risks for retifanlimab was conducted in accordance with Revision 2 to the guideline on GVP Module V – Risk Management Systems (31 March 2017). A careful review of the available data was performed to determine if the identified and potentials risks met the criteria for important in line with the revised GVP Module V. Based on this review, the following risks were not considered to have an impact on the risk-benefit balance of the product and therefore do not qualify for inclusion into the list of safety concerns for the purpose of risk management planning.

Risks with minimal/no clinical impact on patients and that do not impact the risk-benefit profile:

- Fatigue
- Anaemia
- Nausea
- Arthralgia
- Constipation
- Decreased appetite
- Immunogenicity

Known risks with minimial impact on patients given the indicated population and that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- Embryo-fetal toxicity

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks: Immune-Mediated Adverse Reactions

Risk-benefit impact:

In the All Cancer 500mg Q4W Population, immune-mediated adverse events (immune-mediated AEs) occurred in 156 participants (34.5%). The immune mediated AEs were Grade 3 in 38 participants (8.4%), Grade 4 in 6 participants (1.3%), and fatal in 1 participant (PT: interstitial lung disease). Serious immune-mediated AEs occurred in 31 participants (6.9%), and 30 participants (6.6%) had immune-mediated AEs leading to retifanlimab discontinuation.

Taking into account the seriousness and severity of immune-mediated AEs, the clinical actions required to mitigate the risk of immune-mediated AEs in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 ihibitors, immune-mediated adverse reactions is considered an important identified risk.

The risk-benefit balance for retifanlimab remains favourable in relation to the severity of the indication treated, the additional risk minimization measures put in place, and when used in accordance with the proposed SmPC.

Important Identified Risks: Infusion-Related Reactions

Risk-benefit impact:

Infusion-related reactions (IRRs) occurred in 28 participants (6.2%) in the All Cancer 500 mg Q4W Population. IRRs led to retifanlimab infusion interruptions in 4 participants (0.9%) as well as 1 additional participant (0.2%) captured as a "dose delay", and retifanlimab discontinuation in 2 participants (0.4%). In the All Cancer 500 mg Q4W Population, all IRRs were Grade 1 or 2 in severity with the exception of 2 participants (0.4%) with a Grade 3 reaction. Serious IRRs occurred in 3 participants (0.7%) and no IRRs were fatal.

Taking into account the seriousness of infusion-related reactions, the clinical actions required to mitigate the risk of infusion-related reactions in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 ihibitors, infusion-related reactions is considered an important identified risk.

The risk-benefit balance for retifanlimab remains favourable in relation to the severity of the indication treated and when used in accordance with the proposed SmPC.

Important Potential Risks:

There are currently no important potential risks to be included in this RMP.

Missing Information: Long-Term Safety

Risk-benefit impact:

The median duration of retifanlimab treatment was 5.4 months (range: 1 day - 27.0 months) and 31.9% of participants received retifanlimab for > 12 months and 21.9% of participants had received retifanlimab for > 18 months in the All Cancer 500 mg Q4W Population.

At the time of the data cutoff dates for the individual studies, the median duration of safety follow-up in the All Cancer 500 mg Q4W Population was 7.6 months (range: 8 days-30 months).

Taking into account that long-term exposure and long-term follow-up is limited and in an effort to harmonize with other PD-(L)1 inhibitors, long-term safety is considered missing information.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

This section is not applicable as this is an initial RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks: Immune-Mediated Adverse Reactions

Potential mechanisms:

Retifanlimab is a humanized, hinge-stabilized, IgG4κ mAb that recognized human PD-1 and is designed to target PD-1-expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2. The PD-1–PD-L1/L2 inhibitory signaling pathway is one of several known "immune checkpoints" utilized by the immune system to help maintain self-tolerance and modulate the duration and amplitude of physiological immune responses in peripheral tissues. Cancer cells co-opt certain immune checkpoint pathways, including the PD-1 pathway, as a major mechanism of immune evasion or resistance, particularly against T cells that are specific for tumor antigens (Chen and Mellman 2013, Topalian et al 2015, Yao et al 2013). The T lymphocytes hyperactivation induced by ICI generates a specific response directed against tumor antigens, leading to anti-tumor activity in tumor tissues but also side effects in normal tisues. The CD8+ cytotoxic T lymphocytes-mediated cell lysis induces the release of neoantigens, tumor antigens and auto-antigens from normal tissues, respectively. This phenomenon called "epitope spreading" leads to diversification of the T cell repertoire and thus to reduced immune tolerance, which is exacerbated by inhibition of regulator T lymphocytes. Furthermore, the predominant activation of Th1 and Th17T lymphocytes mediated by ICI induced an increased production of pro-inflammatory cytokines such as interferon-γ and interleukine-17 (Passat et al 2018).

Evidence source(s) and strength of evidence:

ICI use is associated with a spectrum of adverse effects related to the mechanism of action. The adverse effects can affect multiple organs of the body and are known as immune-mediated AEs. ICI therapy can usually continue in the presence of mild immune-mediated AEs with close monitoring. However, moderate to severe immune-mediated AEs may be associated with severe delclines in organ function and fatal outcomes have been reported. These events require early detection and proper management (Schneider et al 2021). Taking into account the seriousness and severity of immune-mediated AEs, the clinical actions required to mitigate the risk of immune-mediated AEs in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 ihibitors, immune-mediated adverse reactions is considered an important identified risk.

Characterisation of the risk:

In the All Cancer 500mg Q4W Population, immune-mediated AEs occurred in 156 participants (34.5%). The immune-mediated AEs were Grade 3 in 38 participants (8.4%), Grade 4 in 6 participants (1.3%), and fatal in 1 participant (PT: interstitial lung disease). Serious immune-mediated AEs occurred in 31 participants (6.9%), and 30 participants (6.6%) had immune-mediated AEs leading to retifanlimab discontinuation.

Immune-mediated pneumonitis

In the All Cancer 500 mg Q4W Population, immune-mediated pneumonitis events (PTs: interstitial lung disease, lung infiltration, pneumonitis, and organising pneumonia) occurred in 14 participants (3.1%). Pneumonitis was maximum severity Grade 1 in 3 participants (0.7%), Grade 2 in 6 participants (1.3%), Grade 3 in 4 participants (0.9%), and Grade 5 in 1 participant (0.2%, PT of interstitial lung disease). Six participants (1.3%) had serious pneumonitis. Pneumonitis led to dose delay in 5 participants (1.1%) and discontinuation in 1 participant (0.2%). The median onset time of observed pneumonitis was 100.0 days (range: 43-673 days). Among the 14 participants with pneumonitis, 10 participants (71.4%) received systemic corticosteroids, including 7 participants (50.0%) who received high-dose systemic corticosteroids; 1 participant (7.1%) received inhaled steroids; and no participants received other immunosuppressants. Pneumonitis resolved in 11 participants (78.6%), with a median time to resolution of 37.0 days (range: 9-104 days).

Immune-mediated colitis

In the All Cancer 500 mg Q4W Population, immune-mediated colitis events (PTs: colitis, diarrhea, and immune-mediated enterocolitis) occurred in 12 participants (2.7%). Colitis was maximum severity Grade 1 in 4 participants (0.9%), Grade 2 in 5 participants (1.1%), Grade 3 in 2 participants (0.4%), and Grade 4 in 1 participant (0.2%). Three participants (0.7%) had serious colitis. Colitis led to retifanlimab dose delay in 6 participants (1.3%); and discontinuation of retifanlimab in 4 participants (0.9%). The median onset time of observed colitis was 165.5 days (range: 11-749 days). Among the 12 participants with colitis, 9 participants (75.0%) received systemic corticosteroids, including 5 participants (41.7%) who received high-dose systemic corticosteroids, and 1 participant (8.3%) received other immunosuppressants. Colitis resolved in 8 participants (66.7%), with a median time to resolution of 83.5 days (range: 15-675 days).

Immune-mediated nephritis

In the All Cancer 500 mg Q4W Population, immune-mediated nephritis events (PTs: acute kidney injury, blood creatinine increased, renal failure and tubulointerstitial nephritis) occurred in 9 participants (2.0%). Nephritis was maximum severity Grade 2 in 2 participant (0.4%), Grade 3 in 5 participants (1.1%), and Grade 4 in 2 participants (0.4%). Five participants (1.1%) had serious nephritis. Nephritis led to retifanlimab dose delay in 3 participants (0.7%) and discontinuation of retifanlimab in 5 participants (1.1%). The median onset time of observed nephritis was 176.0 days (range: 15-515 days). Among the 9 participants with nephritis, 6 participants (66.7%) received systemic corticosteroids, including 4 participants (44.4%) who received high-dose systemic corticosteroids; 2 participants (22.2%) received endocrine therapy (insulin); and no participants received other immunosuppressants. Nephritis resolved in 4 participants (44.4%), with a median time to resolution of 22.5 days (range: 9-136 days).

Immune-mediated endocrinopathies

In the All Cancer 500 mg Q4W Population, hypothyroidism (PTs: blood thyroid stimulating hormone increased and hypothyroidism) occurred in 46 participants (10.2%). Hypothyroidism was maximum severity Grade 1 in 24 participants (5.3%) and Grade 2 in 22 participants (4.9%). No participants had serious hypothyroidism. Hypothyroidism led to retifanlimab dose delay in 2 participants (0.4%) and discontinuation of retifanlimab in no participants. The median onset time of observed hypothyroidism was 88.0 days (range: 1-505 days). Among the 46 participants with

hypothyroidism, 1 participant (2.2%) received systemic corticosteroids, 36 participants (78.3%) received endocrine therapy (thyroid), and no participants received high-dose systemic corticosteroids or other immunosuppressants. Hypothyroidism resolved in 15 participants (32.6%), with a median time to resolution of 56.0 days (range: 2-224 days).

In the All Cancer 500 mg Q4W Population, hyperthyroidism (PTs: blood thyroid stimulating hormone decreased and hyperthyroidism) occurred in 26 participants (5.8%). Hyperthyroidism was maximum severity Grade 1 in 14 participants (3.1%) and Grade 2 in 12 participants (2.7%). No participants had serious hyperthyroidism. Hyperthyroidism led to retifanlimab dose delay in 2 participant (0.4%) and discontinuation of retifanlimab in no participants. The median onset time of observed hyperthyroidism was 55.5 days (range: 8-575 days). Among the 26 participants with hyperthyroidism, 4 participants (15.4%) received systemic corticosteroids, 13 participants (50.0%) received endocrine therapy (thyroid), and no participants received high-dose systemic corticosteroids or other immunosuppressants. Hyperthyroidism resolved in 16 participants (61.5%), with a median time to resolution of 74.0 days (range: 15-295 days).

In the All Cancer 500 mg Q4W Population, adrenal insufficiency occurred in 4 participants (0.9%). Adrenal insufficiency was maximum severity Grade 2 in 2 participant (0.4%), and Grade 3 in 2 participants (0.4%). Two participants (0.4%) had serious adrenal insufficiency. Adrenal insufficiency led to dose delay in 1 participant (0.2%) and discontinuation of retifanlimab in no participants. The median onset time of observed adrenal insufficiency was 220.5 days (range: 146-275 days). All 4 participants (100%) received systemic corticosteroids, and no participants received endocrine therapy or other immunosuppressants. Adrenal insufficiency resolved in 1 participant (25.0%), with a time to resolution of 12.0 days.

In the All Cancer 500 mg Q4W Population, thyroiditis (PTs: autoimmune thyroiditis and thyroiditis) maximum severity Grade 1 occurred in 3 participants (0.7%). No participants had serious thyroiditis . Thyroiditis did not lead to dose delay or discontinuation of retifanlimab. The median onset time of observed thyroiditis was 252.0 days (range: 63-306 days). Among the 3 participants with thyroiditis, 2 participants (66.7%) received endocrine therapy (thyroid), and no participants received systemic corticosteroids or other immunosuppressants. Thyroiditis resolved in 1 participant (33.3%), with a time to resolution of 29.0 days.

In the All Cancer 500 mg Q4W Population, hypophysitis occurred in 3 participants (0.7%). Hypophysitis was maximum severity Grade 2 in 2 participants (0.4%) and Grade 3 in 1 participant (0.2%). One participant (0.2%) had serious hypophysitis, and 1 participant (0.2%) had hypophysitis that led to dose delay. One participant (0.2%) had an event that led to discontinuation of retifanlimab. The median onset time of observed hypophysitis was 308.0 days (range: 266-377 days). All 3 participants received systemic corticosteroids, and no participants received high-dose systemic corticosteroids, endocrine therapy, or other immunosuppressants. Hypophysitis resolved in 1 participant (33.3%), with a time to resolution of 6.0 days.

In the All Cancer 500 mg Q4W Population, Type 1 diabetes (PT: diabetic ketoacidosis) maximum severity Grade 3 occurred in 1 participant (0.2%). This event was serious and led to dose delay. The onset time of observed Type 1 diabetes was 284.0 days. The participant received endocrine therapy (insulin) and the event resolved in 6.0 days.

Immune-mediated skin adverse reactions

In the All Cancer 500 mg Q4W Population, immune-mediated skin reactions (PTs: dermatitis, dermatitis bullous, lichenoid keratosis, palmar-plantar erythrodysaesthesia syndrome, pruritus, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic epidermal necrolysis, and toxic skin eruption) occurred in 43 participants (9.5%). Skin reactions were maximum severity Grade 1 in 1 participant (0.2%), Grade 2 in 36 participants (8.0%), Grade 3 in 5 participants (1.1%), and Grade 4 in 1 participant (0.2%). One participant (0.2%) had a serious skin reaction. Skin reactions led to retifanlimab dose delay in 12 participants (2.7%) and discontinuation of retifanlimab in 3 participants (0.7%). The median onset time of observed skin reactions was 86.0 days (range: 2-589 days). Among the 43 participants with skin reactions, 14 participants (32.6%) received systemic corticosteroids, including 8 participants (18.6%) who received high-dose systemic corticosteroids; 24 participants (55.8%) received topical steroids; 1 participant (2.3%) received another systemic immunosuppressant (mycophenolate mofetil); and 1 participant (2.3%) received another topical immunosuppressant (tacrolimus). Skin reactions resolved in 31 participants (72.1%), with a median time to resolution of 37.0 days (range: 3-470 days).

Immune-mediated hepatitis

In the All Cancer 500 mg Q4W Population, immune-mediated hepatitis events (PTs: ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, hepatitis, hepatocellular injury, hyperbilirubinemia, and transaminases increased) occurred in 16 participants (3.5%). Hepatitis was maximum severity Grade 2 in 4 participants (0.9%), Grade 3 in 11 participants (2.4%), and Grade 4 in 1 participant (0.2%). Six participants (1.3%) had serious hepatitis. Hepatitis led to retifanlimab dose delay in 5 participants (1.1%) and discontinuation of retifanlimab in 7 participants (1.5%). The median onset time of observed hepatitis was 70.5 days (range: 8-580 days). Among the 16 participants with hepatitis, 13 participants (81.3%) received systemic corticosteroids, including 12 participants (75.0%) who received high-dose systemic corticosteroids, and 1 participant (6.3%) who received another immunosuppressants (mycophenolate mofetil). Hepatitis resolved in 9 participants (56.3%), with a median time to resolution of 22.0 days (range: 6-104 days).

Other immune-mediated adverse events

In the All Cancer 500 mg Q4W Population, immune-mediated myositis occurred in 3 participants (0.7%), Guillain-Barré syndrome (PTs: demyelinating polyneuropathy and polyneuropathy) occurred in 3 participants (0.7%), immune-mediated pancreatitis occurred in 2 participants (0.4%), uveitis (PTs: iritis and uveitis) occurred in 3 participants (0.7%), immune-mediated musculoskeletal and connective tissue events occurred in 6 participants (1.3%), immune-mediated nervous system events occurred in 2 participants (0.4%), immune-mediated cardiac or vascular events occurred in 1 participant (0.2%), immune-mediated hepatobiliary event occurred in 1 participant (0.2%), immune-mediated myocarditis occurred in 1 participant (0.2%), and immune-mediated ocular event occurred in 1 participant (0.2%)

<u>Risk factors and risk groups:</u>

Recent retrospective studies and a systemic review and meta-analysis reported that a combination of ICIs and other agents, treatment lines of ICI initiation, cycles of ICI administration, body mass index (BMI), derived neutrophil-to-lymphocyte ratio, serum albumin level, history of Type 1 hypersensitivity reactions, c-reactive protein, and smoking status could

be associated with the incidence of immune-mediated AEs (Eun et al 2019, Nuzzo et al 2020, Shimozaki et al 2021, Suazo-Zepeda et al 2021). Some reports also suggest that the incidence of immune-mediated AEs is higher in patients with autoimmune diseases than in those without them; however, the relationship between preexisting autoimmune disorders and the development of immune-mediated AEs remains controversial (Calabrese et al 2018, Abdel-Wahab et al 2018, Abu-Sbeih et al 2020)

Preventability:

Perdictablility of immune-mediated AEs and factors that increase the risk of adverse reactions are not well understood. Routine and additional risk minimization measures outlined in Section Part V along with the European Society of Medical Oncology (ESMO) clinical practice guidelines for the management of toxicities from immunotherapy are in place to minimize the risk immune-mediated adverse reactions.

Impact on the risk-benefit balance of the product:

Given the risk minimization measures outlined in Section Part V along with the ESMO clinical practice guidelines for the management of toxicities from immunotherapy the benefit-risk balance of retifanlimab remains favourable in relation to the severity of the indication treated.

Public health impact:

There is no public health impact expected. Immune-mediated AEs would affect the individual on treatment only and are manageable with established guidelines.

Important Identified Risks: Infusion Related Reactions

Potential mechanisms:

Mild to moderate infusion reactions are associated with chills, fever, mild hypotension, dyspnea and rash. Severe reactions are less common and are, amongst other symptoms, associated with severe hypotension, anaphylaxis and cardiac dysfunction. An infusion reaction usually starts within 30 to 120 min after the start of administration of the monoclonal antibody, but delayed infusion reactions at up to 24 hours after infusion have been observed. Most infusion reactions to monoclonal antibodies occur by the binding of the monoclonal antibody to the target cell which releases cytokines into circulation and causes symptoms (Rombouts et al 2020).

Evidence source(s) and strength of evidence:

IRRs are common adverse drug reactions (ADRs) with monoclonal antibodies. Symptoms are temporally related to the drug administration and may range from symptomatic discomfort to fatal events (Doessegger and Banholzer 2015).Taking into account the seriousness of IRRs, the clinical actions required to mitigate the risk of IRRs in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 ihibitors, IRRs is considered an important identified risk.

Characterisation of the risk:

IRRs occurred in 28 participants (6.2%) in the All Cancer 500 mg Q4W Population. IRRs led to retifanlimab infusion interruptions in 4 participants (0.9%), as well as 1 additional participant (0.2%) captured as a “dose delay”, and retifanlimab discontinuation in 2 participants (0.4%). In the All Cancer 500 mg Q4W Population, all IRRs were Grade 1 or 2 in severity with the

exception of 2 participant (0.4%) with a Grade 3 reaction. Serious IRRs occurred in 3 participants (0.7%) and no IRRs were fatal.

Risk factors and risk groups:

No specific risk factors or risk groups are known. All patients are potentially at risk for IRRs.

Preventability:

Patients that have experienced an IRR with a foreign protein are at at risk group for IRRs. Routine risk minimization measures outlined in Section Part V are in place to minimize the risk IRRs.

Impact on the risk-benefit balance of the product:

Given the frequency and severity of IRRs seen with retifanlimab and risk minimization measures outlined in Section Part V the benefit-risk balance of retifanlimab remains favourable in relation to the severity of the indication treated.

Public health impact:

There is no public health impact expected. IRRs would affect the individual on treatment only and are manageable.

Important Potential Risks:

There are currently no important potential risks included in this RMP.

SVII.3.2 Presentation of the Missing Information

Missing information: Long-Term Safety

Evidence source:

The median duration of retifanlimab treatment was 5.4 months (range: 1 day-27.0 months) and 31.9% of participants received retifanlimab for > 12 months, and 21.9% of participants had received retifanlimab for > 18 months in the All Cancer 500 mg Q4W Population. Duration of treatment was limited to 2 years in all studies.

At the time of the data cutoff dates for the individual studies, the median duration of safety follow-up in the All Cancer 500 mg Q4W Population was 7.6 months (range: 8 days – 30.0 months).

Population in need of further characterisation:

Participants treated with retifanlimab > 12 - 24 months.

PART II: MODULE SVIIISUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-Mediated Adverse Reactions Infusion-Related Reactions

Summary of safety concerns	
Important potential risks	None
Missing information	Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

There are currently no specific adverse reaction follow-up questionnaires being used for retifanlimab.

Other forms of routine pharmacovigilance activities:

There are currently no other forms of routine pharmacovigilance activities for retifanlimab.

III.2 Additional Pharmacovigilance Activities

There are currently no additional pharmacovigilance activities for retifanlimab.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are currently no additional pharmacovigilance activities for retifanlimab.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Immune-mediated adverse reactions	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for dose modifications for immune-mediated adverse reactions are included in SmPC sections 4.2 and 4.4 Signs and symptoms of immune-mediated adverse reactions and potential dose modifications are included in PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription
Infusion-related rections	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for prophylaxis and dose modifications for infusion-related reactions are included in SmPC sections 4.2 and 4.4 Signs and symptoms of infusion-related reactions and potential dose modifications are included in PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription
Long term safety data	Routine risk communication: N/A Routine risk minimisation activities recommending specific clinical measures to address the risk: N/A Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription

V.2 Additional Risk Minimization Measures

Patient Card

Objectives:

The objective of the patient card is to miminise the risk of immune-mediated adverse reactions and optimize the benefit-risk balance of retifanlimab. The aim of this tool is to ensure that information regarding the patient's treatment with retifanlimab and its important risk of immune-medaited adverse reactions are held by the patient at all times and reaches the relevant healthcare

professionals as appropriate. The information on the patient card is focused on signs and symptoms of immune-mediated adverse reactions and the best course of action to be taken by the patient and relevant healthcare professional.

Rationale for the additional risk minimisation activity:

Taking into account the seriousness and severity of immune-mediated adverse reactions, need for early diagnosis, and the clinical actions required to mitigate the risk of immune-mediated adverse reactions s in patients being treatd with PD-(L)1 inhibitors, including retifanlimab, additional risk minimisation activities are deemed necessary. In order to harmonize with other PD-(L)1 ihibitors, educational material in the form of a Patient Card was chosen as the appropriate additional risk minimization measure.

Target audience and planned distribution path:

This patient card that includes information regarding the patient's treatment with retifanlimab and its important risk of immune-mediated adverse reactions are held by the patient at all times and are to be used to inform relevant healthcare professionals as appropriate. All prescribers of retifanlimab should inform patients about the Patient Card, explaining what to do should they experience any symptom of immune-mediated adverse reactions. The physician will provide the Patient Card to each patient.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine PV activities will provide information to allow assessment on any changes of the known occurrence, severity, and outcome of immune-mediated adverse reactions for Zynyz and will be reported in the PBRER.

V.3 Summary of Risk Minimization Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-Mediated Adverse Reactions	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Infusion Related Reactions	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long Term Safety	Routine risk minimisation measures: Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR Zynyz (retifanlimab)

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

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

This summary of the RMP for Zynyz 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 Zynyz's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Zynyz is authorised for first-line treatment of adult patients with Merkel cell carcinoma (see SmPC for the full indication). It contains retifanlimab as the active substance and it is administered by IV infusion.

Further information about the evaluation of Zynyz's benefits can be found in Zynyz's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

Measures to minimise 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that

immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of Zynyz, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risk, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 Zynyz is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Zynyz are risks that need special risk management activities to further investigate or minimise 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 Zynyz. 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 II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Immune-mediated adverse reactions Infusion-related reactions
Important potential risks	None
Missing information	Long term safety data

II.B Summary of Important Risks

Important identified risk: Immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	ICI use is associated with a spectrum of adverse effects related to the mechanism of action. The adverse effects can affect multiple organs of the body and are known as immune-mediated AEs. ICI therapy can usually continue in the presence of mild immune-mediated AEs with close monitoring. However, moderate to severe immune-mediated AEs may be associated with severe declines in organ function and fatal outcomes have been reported. These events require early detection and proper management (Schneider et al 2021). Taking into account the seriousness and severity of immune mediated AEs, the clinical actions required to mitigate the risk of immune-mediated AEs in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize

Important identified risk: Immune-mediated adverse reactions	
	with other PD-(L)1 ihibitors, immune-mediated adverse reactions is considered an important identified risk.
Risk factors and risk groups	Recent retrospective studies and a systemic review and meta-analysis reported that a combination of ICIs and other agents, treatment lines of ICI initiation, cycles of ICI administration, BMI, derived neutrophil-to-lymphocyte ratio, serum albumin level, history of Type 1 hypersensitivity reactions, c-reactive protein, and smoking status could be associated with the incidence of immune-mediated AEs (Eun et al 2019, Nuzzo et al 2020, Shimozaki et al 2021, Suazo-Zepeda et al 2021). Some reports also suggest that the incidence of immune-mediated AEs is higher in patients with autoimmune diseases than in those without them; however, the relationship between preexisting autoimmune disorders and the development of immune-mediated AEs remains controversial (Calabrese et al 2018, Abdel-Wahab et al 2018, Abu-Sbeih et al 2020)
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: Patient Card

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	Infusion related reactions are common ADRs with monoclonal antibodies. Symptoms are timely related to the drug administration and may range from symptomatic discomfort to fatal events (Doessegger and Banholzer 2015).Taking into account the seriousness of infusion-related reactions, the clinical actions required to mitigate the risk of infusion-related reactions in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 inhibitors, infusion-related reactions is considered an important identified risk.
Risk factors and risk groups	No specific risk factors or risk groups are known. All patients are potentially at risk for IRRs.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: None

Missing information: Long term safety data	
Risk minimisation measures	Routine risk minimisation measures: Legal status Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

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

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Zynyz.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Draft key messages of the additional risk minimisation measures

Prior to the launch of Zynyz in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The purpose of the educational programme is to minimise the risk of immune-mediated adverse reactions and optimize the risk-benefit balance of Zynyz. The aim of this tool is to ensure that information regarding the patient's treatment with Zynyz and its important risk of immune-mediated adverse reactions are held by the patient at all times and reaches the relevant healthcare professionals as appropriate. The information on the patient card is focused on signs and symptoms of immune-mediated adverse reactions and the best course of action to be taken by the patient and relevant healthcare professional.

The MAH shall ensure that in each Member State where Zynyz is marketed, all healthcare professionals who are expected to prescribe Zynyz have access to/are provided with the following educational materials:

- Package leaflet
- Patient card
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Zynyz
  - That Zynyz treatment may increase the risk of: Immune-mediated adverse reactions
  - Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
  - Contact details of the Zynyz prescriber