EU RMP	
Drug Substance	Sodium zirconium cyclosilicate
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) For LOKELMA™ (Sodium Zirconium Cyclosilicate)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV in the EU.

Administrative Information

Rationale for submitting an updated RMP:

The LOKELMA EU-RMP has been updated to include a new safety concern of "New Onset Cardiac Failure" as an Important Potential Risk.

Summary of significant changes in this RMP

Part I

Updated to remove the requirement for additional monitoring in the EU.

Part II SIII

Updated with clinical trial details from studies REALIZE K (D9480C00018) and Stabilize CKD (D9488C00001) and Dialize outcome (D9487C00001).

Part II SV

Updated with post marketing exposure details.

Part II SVII

Updated with new safety concern of "New onset cardiac failure" as an Important Potential. Risk.

Part II SVIII

New safety concern of " New onset cardiac failure" added as an Important Potential risk.

Part III

Updated according to Part II SVII.

Part V

Updated according to Part II SVII

Part VI

Updated according to Part II SVII.

Part VII

Updated according to Part II SVII

Other RMP versions under evaluation	**Version Number**: None **Submitted**: NA **Procedure number**: NA
Details of currently approved RMP	**Version Number**: 2 **Approved with procedure**: EMEA/H/C/004029/II/0013 **Date of approval:** 28 April 2020

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
CDS	Core Data Sheet
CPRD	Clinical Practice Research Datalink
CPS	Calcium Polystyrene Sulfonate
DSUR	Development Safety Update Report
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EU RMP	European Union Risk Management Plan
LRMP	Local Risk Management Plan
MedDRA	Medical Dictionary for Regulatory Activities
PBRER	Periodic Benefit Risk Evaluation Report
PT	(MedDRA) Preferred Term
RAASi	Renin Angiotensin Aldosterone System inhibitors
RASi	Renin Angiotensin System inhibitors
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
PSUR	Periodic Safety Update Report
S-K	Serum Potassium
SCREAM	Stockholm CREAtinine Measurements
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA Query
SPS	Sodium Polystyrene Sulfonate
SZC	Sodium Zirconium Cyclosilicate
TID	Ter In Die (three times a day)

1 PART I: PRODUCT OVERVIEW

Table 1-1 Product Overview

Active substance	Sodium Zirconium Cyclosilicate (SZC)
Pharmacotherapeutic group (ATC code)	Drugs for treatment of hyperkalaemia and hyperphosphatemia - V03AE10
Marketing Authorisation Holder	AstraZeneca AB

Table 1-1 Product Overview

Medicinal products to which this RMP refers	1
Invented name in the European Economic Area	LOKELMA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: SZC is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations.
	Summary of mode of action: SZC is highly selective for potassium ions, even in the presence of other cations such as calcium and magnesium, in vitro. Sodium zirconium cyclosilicate captures potassium throughout the entire gastrointestinal tract and reduces the concentration of free potassium in the gastrointestinal lumen, thereby lowering serum potassium levels (S-K) and increasing faecal potassium excretion to resolve hyperkalaemia.
Hyperlink to the Product Information	**LOKELMA Product Information**
Indication in EEA	**Current**: LOKELMA is indicated for the treatment of hyperkalaemia in adult patients
	Proposed: Not applicable
Dosage in the EEA	**Current**: <u>Correction phase</u> The recommended starting dose of LOKELMA is 10 g, administered three times a day orally as a suspension in water. When normokalaemia is achieved, the maintenance regimen should be followed (see below). Typically, normokalaemia is achieved within 24 to 48 hours. If patients are still hyperkalaemic after 48 hours of treatment, the same regimen may be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered. <u>Maintenance phase</u> When normokalaemia has been achieved, the minimal effective dose of LOKELMA to prevent recurrence of hyperkalaemia should be established. A starting dose of 5 g once daily is recommended, with possible titration up to 10 g once daily, or down to 5 g once every other day, as needed, to maintain a normal potassium level. No more than 10 g once daily should be used for maintenance therapy.
Pharmaceutical form(s) and strengths	Powder for oral suspension, 5 g and 10 g.

Table 1-1 Product Overview

Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

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

2.1.1 Hyperkalaemia

Incidence

In a retrospective cohort study using the Clinical Practice Research Datalink (CPRD) from the UK, the crude incidence (per 1000 patient-years) of hyperkalaemia was reported as 246.02, 62.66 and 15.00 with a S-K of ≥5.0 mmol/L to < 5.5 mmol/L, ≥5.5 mmol/L to < 6.0 mmol/L and ≥6.0 mmol/L, respectively (Furuland et al 2018). In heart failure (HF) patients experiencing at least one episode of hyperkalaemia when defined as S-K ≥5.0, ≥5.5, or ≥6.0 mmol/L, corresponding crude rates of hyperkalaemia were 323.5, 79.9, and 16.1 episodes per 1000 patient-years, respectively (Linde et al 2019).

In an observational study from the Stockholm CREAtinine Measurements (SCREAM) project, including adult healthcare users (n=364,955) in the region of Stockholm, Sweden, the incidence rate of hyperkalaemia (S-K >5 mmol/L) was 49.9/1000-person years among patients with at least one creatinine and one potassium measurement, with considerably higher rates observed in those with diabetes, lower Estimated Glomerular Filtration Rate (eGFR), myocardial infarction, heart failure or Renin-Angiotensin-Aldosterone System inhibitors (RAASi) users. Over the 3-year period, hyperkalaemia occurred in 25,461 (7%) individuals. Most cases (65%) had only one event during follow-up. Hyperkalaemia recurrence was less common (35% of cases). Moderate/severe hyperkalaemia (S-K>5.5 mmol/L) occurred in 9059 (2.5%) individuals (Nilsson et al 2017). Trevisan et al, using the SCREAM cohort identified 13,726 individuals initiating mineralocorticoid receptor antagonist therapy during 2007-2010 with a median age of 73 years, 53% women and median plasma S-K of 3.9 mmol/L. Within a year, 18.5% experienced at least one detected hyperkalaemia (S-K > 5.0 mmol/L), the majority within the first 3 months of therapy. As a comparison, hyperkalaemia was detected in 6.4% of propensity-matched new beta-blocker users (Trevisan et al 2018).

A population-based analysis of CKD patients identified from Danish healthcare and laboratory databases reported that the incidence of hyperkalaemia was 70, 27 and 12 per 1000-person years when defined as S-K ≥5.0, ≥5.5, and ≥6.0 mmol/L, respectively (Thomsen et al 2017). Of 68,601 Danish individuals with diabetes the incidence rate of hyperkalaemia was 40 per 1000 person-years (Thomsen et al 2018 (2)). In patients with chronic kidney disease (CKD) and first hospitalization for HF, the incidence of hyperkalaemia was 178, 72.5 and 31.7 1000-

person years when defined as S-K ≥5.0, ≥5.5, and ≥6.0 mmol/L, respectively (Thomsen et al 2018 (1).

Prevalence:

A study based on hospital admissions in Ontario, Canada, hyperkalaemia (defined by ICD-10 code) was present in 2.6% of emergency room visits and 3.5% of hospital admissions (Fleet et al 2012). In a recent study using data from the National Health and Nutrition Examination Survey, reported the overall prevalence of 564 (95% CI: 482-646) per 100,000 persons, with the prevalence increased from 278 per 100,000 persons aged 35-49 years to 2394 per 100,000 persons aged >75 years. In multivariable analyses, age, chronic kidney disease, heart failure, and use of RAASi were important predictors of hyperkalaemia (Woolley et al 2016). Data from MarketScan estimated 3.7 million US adults had hyperkalemia in 2014, and this prevalence rate has increased since 2010. In patients with CKD and/or heart failure, the annual prevalence of hyperkalemia was 6.35% in 2014, and about half of all patients with hyperkalemia have either CKD and/or heart failure (Betts et al 2018)

Demographics of the population in the indication –age, gender, racial and risk factors for the disease:

The critical risk factors for developing hyperkalaemia were the presence of diabetes, heart failure, higher protein intake, lower eGFR (more advanced CKD), lower serum bicarbonate, white race, and the use of RAASi therapy. The risk is highest among patients with multiple risk factors (Collins et al 2017;Furuland et al 2018; Linde et al 2019; Nilsson et al 2017;Palaka et al 2018;Thomsen et al 2018 (1);Thomsen et al 2018 (2); Thomsen et al 2017; Jain et al 2012).

Trevisan et al. using Swedish data reported CKD, older age, male sex, heart failure, peripheral vascular disease, diabetes and concomitant use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and diuretics were associated with increased hyperkalaemia risk (Trevisan et al 2018). Another Swedish study using the SCREAM database reported using multivariable logistic regression analysis, female sex (odds ratio (OR) 0.79, 95% confidence intervals (CIs): 0.77-0.81) and baseline use of loop/thiazide diuretics (0.94, 0.90-0.97) associated with lower hyperkalaemia risk. Older age categories (Age 45-64: 1.52, 1.42-1.63; Age 65-74: 1.82, 1.69-1.95; Age >=75 years: 1.87, 1.74-2.01; reference age group: 18-44), lower eGFR strata (eGFR G3: 2.14, 2.07-2.22; eGFR G4+: 5.6, 5.24-5.98; reference category eGFR G1-2), diabetes mellitus (1.73, 1.67-1.79), heart failure (1.14, 1.09-1.19) and baseline use of Angiotensin Converting Enzyme inhibitors (1.51, 1.46-1.57), Angiotensin Receptor Blockers (1.21, 1.17-1.26) and Mineralocorticoid Receptor Antagonists (1.66, 1.41-1.95) associated with higher hyperkalaemia risk (Nilsson et al 2017).

In an analysis of 4649 patients of the German Chronic Kidney Disease study with an estimated glomerular filtration rate (eGFR) of 30-60 ml/min or overt proteinuria, greater

proteinuria (OR 1.66, 95%CI 1.29-2.10 for >300 mg/l; reference group: <30 mg/L), lower eGFR (OR 3.45, 95%CI 2.56-4.70 for 30-44 ml/min; OR 1.88, 95%CI 0.97-1.83 for 45-59 ml/min,; OR 5.82, 95%CI 4.11-8.25 for < 30ml/min; reference category: >60 ml/Min), therapy with inhibitors of the renin-angiotensin system (RAASi) (OR 1.88, 95%CI 1.43-2.47) for single RAASi; OR 2.81 (95%CI 1.94-4.09) for dual RAASi) were associated with greater S-K levels. Of note, diabetes mellitus (36% of German Chronic Kidney Disease study patients) was not found to be associated with S-K (Schneider et al 2017).

In an analysis of 19,194 patients with incident heart failure, significant risk factors for hyperkalaemia were: renal failure (OR 3.81; 95% CI 3.29–4.42), type II diabetes (OR 1.52; 95% CI 1.31–1.75), valvular heart disease (OR 1.28; 95% CI 1.06–1.54), and current use of potassium-sparing diuretics (OR 3.01; 95% CI 2.61–3.48), Angiotensin Converting Enzyme inhibitors (OR 1.70; 95% CI 1.41 – 2.04), trimethoprim (OR 2.82; 95% CI 1.88–4.23), non-steroidal anti-inflammatory drugs (OR 1.41; 95% CI 1.11 –1.79), and several drug combinations (Michel et al 2015) .In Denmark, people who developed hyperkalaemia had a higher prevalence of chronic kidney disease [prevalence ratio 1.74 (95% CI 1.68-1.81)], heart failure [prevalence ratio 2.35 (95% CI 2.18-2.54)], use of angiotensin-converting enzyme inhibitors [prevalence ratio 1.24 (95% CI 1.20-1.28)], use of spironolactone [prevalence ratio 2.68 (95% CI 2.48-2.88)] and potassium supplements [prevalence ratio 1.59 (95% CI 1.52-1.67)]. In people with diabetes who developed hyperkalaemia, 31% were acutely hospitalized within 6 months before hyperkalaemia, increasing to 50% 6 months after hyperkalaemia [before-after risk ratio 1.67 (95% CI 1.61-1.72)]. The 6-month mortality rate after hyperkalaemia was 20%. Compared with matched individuals without hyperkalaemia, the hazard ratio for death was 6.47 (95% CI 5.81-7.21) (Thomsen et al 2018 (1)).

The main existing treatment options:

Treatment and prevention of hyperkalaemia includes dose reduction or elimination of medications that may increase potassium levels, dietary limitations to reduce K intake, vigorous use of diuretic therapy, use of drugs including calcium gluconate, insulin, Albuterol (Ventolin), Furosemide (Lasix), bicarbonate, sodium polystyrene sulfonate (Sodium Polystyrene Sulfonate (SPS), Kayexalate, Resonium), and calcium polystyrene sulfonate (Calcium Polystyrene Sulfonate (CPS), Resonium Calcium) and patiromer (Veltassa), drugs which may have severe side effects (Hollander-Rodriguez et al 2006; Ingelfinger et al 2015).

SZC is a stable, inorganic compound that increases the gastrointestinal excretion of potassium. Unlike the currently available products for the treatment of hyperkalaemia by increasing the gastrointestinal excretion of potassium (SPS, CPS and patiromer), SZC has a high capacity and specificity for binding potassium ions. However, SPS and CPS are approved only for short-term treatment of hyperkalaemia. Moreover, these products are non-specific for potassium and they have the potential to affect other electrolytes. They have been reported to cause hypomagnesaemia, hypocalcaemia (SPS), hypercalcaemia (CPS) and sodium overload

(SPS). In addition, they are not suitable for continuous maintenance treatment due to poor gastrointestinal tolerability, and they require administration with a laxative to avoid severe constipation (Castillo-Cejas et al 2013; Harel et al 2013; Sterns et al 2010; Watson et al 2012; Yuan et al 2013).

Current management of hyperkalaemia with S-K above 6.0 mmol/L at the emergency department has not been well studied previously (Rossignol et al 2016), but frequently includes administration of insulin and glucose to shift extracellular potassium to the intracellular space. The effect is rapid and substantial, but only lasts for 4 to 6 hours, and therefore further therapies are required, e.g. haemodialysis or potassium binding drugs. The use of insulin and glucose as the mainstay of therapy is recommended by clinical guidelines such as the American Heart Association guidelines from 2005, and in recent literature (Kovesdy 2015; Li and Vijayan 2014; Rossignol et al 2016).

Maintenance Haemodialysis Treatment

Hyperkalaemia patients receiving maintenance haemodialysis with a high predialysis S-K level are treated with a low dialysate potassium concentration (Abuelo et al 2018; Brunelli et al 2018; Fried et al 2017; Karaboyas et al 2017). However, the serum-to-dialysate S-K gradient requires careful management due to a reported increased risk of all-cause hospitalisations and emergency department visits where S-K gradients are higher (Brunelli et al 2018; Karaboyas et al 2017). IV insulin use has also been reported to treat hyperkalaemia in patients receiving maintenance haemodialysis (Li and Vijayan 2014). Jadoul et al. report the use of sodium-based potassium binding resins such as SPS, in Dialysis Outcomes and Practice Patterns Study centres in Belgium, Canada, France, Italy, and Sweden; the results suggest that K resin use may effectively lower serum K, although at the expense of somewhat higher phosphataemia and greater interdialytic weight gain. There was no clear association of mortality and these potassium binders (Jadoul et al 2014).

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

Potassium homeostasis is essential for maintaining the cellular membrane potential and thus, hyperkalaemia impairs neuromuscular, cardiac and gastrointestinal function. Hyperkalaemia, defined as an elevated level of S-K above 5.0 mmol/L often presents without symptoms or with non-specific symptoms including malaise, confusion, muscle weakness or signs of cardiac arrhythmias such as palpitations, bradycardia, or tachycardia (Henneman et al 2016). The risk of hyperkalaemia varies significantly from the published studies, largely due to differences in the study populations, various definitions used in the studies, as well as the differences in the frequency of potassium monitoring. Recent real-world evidence studies have suggested a U-shape association between a S-K measurement and an increased risk of adverse clinical outcomes with both decreasing and increasing S-K levels (hypokalaemia and hyperkalaemia) outside the normal range of S-K 3.5-5.0 mmol/L in the general population

(Chen et al 2016; Collins et al 2017; Einhorn et al 2009; Furuland et al 2018; Gasparini et al 2018;Horne et al 2019; Hughes-Austin et al 2017; Kovesdy 2015; Linde et al 2019; Luo et al 2016; Núñez et al 2018; Rosano et al 2018; Xu et al 2018).

Mortality increases both with decreasing and increasing S-K levels outside the normal range of S-K 3.5-5.0 mmol/L.

Figure 2-1 Relationship between abnormal potassium levels and mortality

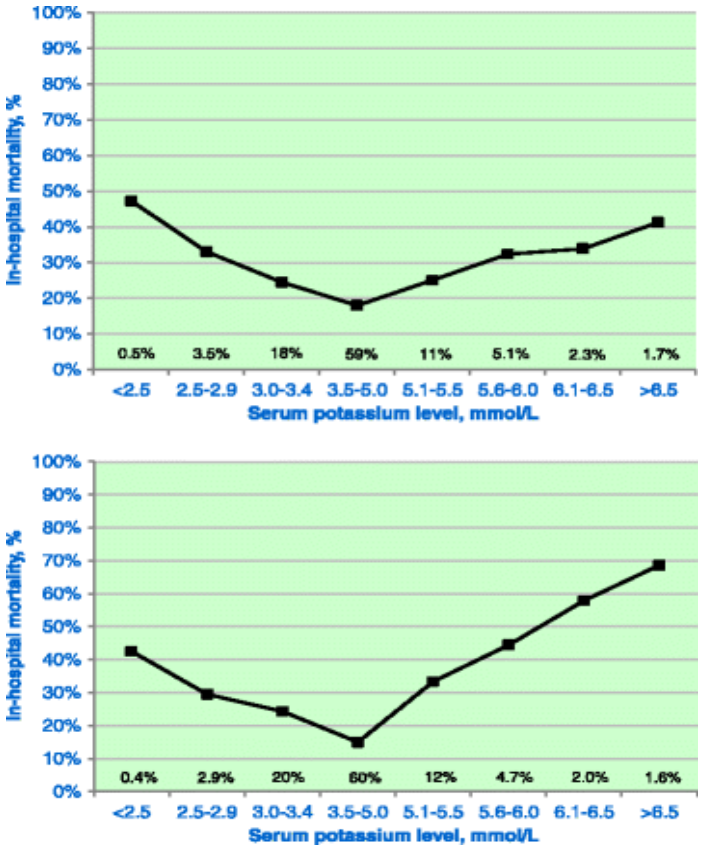

Figure 2-1, illustrates the relationship between abnormal serum potassium levels and mortality during the first 24 hours of intensive care unit admission (early phase; upper panel) and days 2 through 7 (late phase; lower panel) in 22347 patients with 2276 in-hospital deaths (21.8%) (Hessels et al 2015).

The table below shows the incidence rates of clinical outcomes per 100 person-years following the first episode of hyperkalaemia in a cohort of English patients seeking healthcare using data from CPRD primary care database linked to the Hospital Episodes Statistics database (Horne et al 2019

Horne L, Ashfaq A, MacLachlan S, Sinsakul M, Qin L, LoCasale R, Wetmore JB. Epidemiology and health outcomes associated with hyperkalemia in a primary care setting in England. BMC Nephrology. 2019;20;85.

Horne et al 2017).

Table 2-1 Incidence rates of clinical outcomes per 100 person-years based upon severity of hyperkalaemia event

Outcome	Overall	Severity if hyperkalaemia episode		
		Mild	Moderate	Severe
Cardiac arrhythmia	1.07	1.05	1.13	1.83
Cardiac arrest	0.14	0.13	0.17	0.44
All-cause mortality	2.73	2.51	3.83	12.57
Heart failure	0.61	0.60	0.64	1.38
Decline in kidney function	6.68	6.54	7.36	14.61
All-cause hospitalization	14.14	14.05	15.53	28.93

SZC is a drug with a unique mode of action targeting a condition which may be an outcome for a variety of diseases; hence, diagnoses that potentially might be identified as the cause may also be presented as co-morbidities.

Important co-morbidities:

- Diabetes
- Chronic kidney disease
  - Dialysis dependent
  - Non-dialysis dependent
- Heart failure
- Hypertension

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

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

2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Decreased serum aldosterone, increased serum bicarbonate, increased urine sodium excretion and increased urine pH were observed in toxicology studies in dogs at highest dose level. Degenerative and inflammatory changes in kidney and lipid vacuolation in adrenal cortex,

considered secondary to hypokalaemia, were observed after chronic administration at very high dose levels in dogs (not seen in rats). Potassium supplementation helped reduce the incidence and/or magnitude of hypokalaemia and its associated renal and adrenal effects.

Reproductive/developmental toxicity

No key findings identified.

Genotoxicity

No key findings identified.

Carcinogenicity

No studies were conducted.

2.2.2 Safety pharmacology

No standalone studies conducted; safety pharmacology endpoints included in repeat dose toxicity studies.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The tables below, Table 2-2,Table 2-3, and Table 2-4 present clinical trial exposure to LOKELMA until data lock point 31 December 2024. 5781 patients in total have received at least one dose of LOKELMA. The exposure data is from studies ZS-002, ZS-003, ZS-004, ZS-004E, ZS-005, ZS-006, ZS-009, D9480C00002 (HARMONIZE GLOBAL), D9482C00002 (J-DFS), D9483C00001 (CHINA PD Study), D9480C00005 (ENERGIZE), D9480C0006 (DIALIZE), D9480C00001 (HARMONIZE ASIA), D9480C00014 (GRAZE), D9480C00018 (REALIZEK), D9480C00022 (NEUTRALIZE) ,D9482C00001, D9484C00001(PRIORITIZE HF), D9485C00001, D9487C00001 (DIALIZE-Outcomes), D9488C00001(STABILIZE-CKD). Patients participating in crossover studies are counted once for each distinct treatment (regardless of dose) received.

The different durations times of exposure to LOKELMA are presented in Table 2-2

Table 2-2 Duration of exposure

Duration of exposure	Patients	Person Time (years)
1-3 days	1023	4.86
4-30 days	1243	67.29
31-90 days	840	148.04
91-180 days	627	204.09
181-270 days	364	220.96
271-360 days	293	257.85
> 360 days	1391	1823.22

Table 2-2 Duration of exposure

Duration of exposure	Patients	Person Time (years)
Total	5781	2726.31

The exposure by age group and gender is presented in the below Table 2-3. A substantial proportion of females received LOKELMA across all age groups, and the time adjusted exposure of females was comparable below and above 65 years of age.

Table 2-3 Age group and gender

	Patients (N)		Person Time (years)	
Age group	**M**	**F**	**M**	**F**
Adults (e.g. 18-64 years)	1890	1191	972.46	593.54
Elderly people	1703	997	735.42	424.90
65-74 years	1004	618	451.84	293.02
75-84 years	619	325	252.77	117.17
85+ years	80	54	30.82	14.71
Total	3593	2188	1707.88	1018.43

M: Male F: Female

The exposure of LOKELMA by ethnic origin is presented in the below Table 2-4. The majority of the population are white (58%), followed by Asian and Black or African-American (30% and 8%, respectively).

Table 2-4 Race

Race	Patients (N)
WHITE	3363
ASIAN	1710
BLACK OR AFRICAN AMERICAN	466
OTHER	131
AMERICAN INDIAN OR ALASKA NATIVE	66
NOT REPORTED	25
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	12
MULTIPLE	8
Total	5781

2.4 MODULE SIV: Populations not studied in clinical trials

2.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Exclusion Criteria

Patients on dialysis

Reason for exclusion: Patients on maintenance dialysis are prone to a high fluctuation of potassium and therefore would confound results in pivotal studies. This subpopulation has subsequently been studied separately in study D9480C00006 (DIALIZE).

Is it considered to be included as missing information: No

Rationale:

Post-approval, Study D9480C00006; *A multicentre, prospective, randomized, double blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalaemia with SZC,* has reported and the results from the study confirm that the safety profile in patients on dialysis is in line with the established safety profile for LOKELMA. Therefore, 'patients on dialysis' is not considered missing information.

Pregnant and breastfeeding patients

Reason for exclusion: Pregnant and breastfeeding patients were excluded from the pivotal studies according to common practice.

Is it considered to be included as missing information: No

Rationale: Pre-clinical data have not indicated any direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development. Due to its physicochemical properties, LOKELMA is not systemically absorbed and is not thus expected to be excreted in breast milk (see SmPC 4.6). Although some differences may occur due to physiological changes in the functionality in the gastrointestinal tract, it is not anticipated that the safety profile during pregnancy would be different (Baron et al 1993). There are no data from the use of LOKELMA in pregnant women. It is not anticipated that there will be significant use of LOKELMA in pregnant and/or breastfeeding women based on guidance in the SmPC which states, "As a precautionary measure, it is preferable to avoid the use of LOKELMA during pregnancy". In addition, there is no evidence from animal studies that the safety profile in pregnant and breastfeeding women is different (see SmPC 4.6, 5.3). Therefore, data of pregnancy and breastfeeding are not relevant to specify as missing information in the RMP.

Study subjects < 18 years

Reason for exclusion: To establish a robust adult safety profile for LOKELMA prior to the initiation of the paediatric development programme. The paediatric population was not excluded from the clinical program due to any particular safety concern.

Is it considered to be included as missing information: No

Rationale: Use in children under 18 years of age is not indicated for LOKELMA, therefore this population is not relevant for the approved indication.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 2-5 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	
Patient with relevant comorbidities:	
Patients with hepatic impairment	Exposure data for the population are not available.
Patients with Chronic Kidney Disease [a]	N=1443
Patients with Heart Failure [a]	N=297
Patients with Diabetes Mellitus [a]	N=1364
Patients with hypertension [a]	N=1966
Immunocompromised patients	Exposure data for this population are not available
Patients with a disease severity different from inclusion criteria in clinical trials	Exposure data for this population are not available
Patients with relevant different ethnic origin	Patients of Japanese origin/ethnicity are included in the clinical programme. Subjects of Chinese origin/ethnicity were included in the China PD study.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients on maintenance dialysis	N=96
The table does not include any small number of subjects who have been included in the study outside any exclusion criteria.	

[a] These subpopulations were defined by the SMQs (narrow).

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on SZC's monthly actual ex-factory sales volume from each local affiliate. These data represent all SZC formulation delivered to various distribution channels (e.g., wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number 20 sachet packs. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient took 1 sachet of SZC a day. Therefore, a patient-year worth of exposure is calculated by multiplying 1 sachet per day by 365 days (per patient-year).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to SZC. More detailed patient-level data (eg, gender, ethnicity, age category, off-label use, specific populations, etc) are not available.

2.5.2 Exposure

The cumulative global post-marketing patient exposure to SZC (5 g and 10 g sachet), since launch 22 March 2018 to 29 February 2024, has been estimated to be approximately 335659 patient-years.

Approximately 14.40% of the worldwide distribution was in Europe, 27.48% was in Japan, 38.85% was in North America and 19.26 was in international.

The cumulative regional patient exposure figures are presented in Table 2-6

Table 2-6 SZC cumulative sales (in patient-years) by region

Formulation	Europe	International	North America	Japan	Total
LOKELMA Sachet	17647955	23598883	47596266	33672436	122515540

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

LOKELMA is not expected to be used for illegal purposes.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

The content of this section 2.7.1 presents the position at the time of the initial RMP (Version 1), it will not be updated.

2.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

New Onset Cardiac failure is a new important potential risk

A pooled analysis of eight clinical trials was conducted to assess the potential risk of heart failure associated with treatment using SZC. Due to variations in study designs, the analysis was divided into three distinct pools: (1) placebo-controlled titrated dose studies, including Stabilize CKD, Realize-K, and Prioritize HF; (2) single-arm studies, consisting of ZS-005 and Japan-LTS; and (3) placebo-controlled fixed dose studies, which included ZS-004, Harmonize-Global, and Harmonize-Asia. Differences in heart failure were compared both on absolute scale, difference in Kaplan-Meier (KM) estimates, and relative scale, hazard ratio (HR). Initially the risk for heart failure was explored within the subgroups of prior/no-prior HF at baseline, then within subgroups of patients with prior heart failure at baseline. The analysis suggested that the risk of new-onset heart failure remains unclear, but at this time there is no reasonable possibility of a causal relationship between SZC and new onset of heart failure. However, an increased risk of heart failure worsening with SZC in patients with a history of heart failure was observed.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk:

Not applicable

Important Potential Risk: New Onset Cardiac Failure

Potential mechanisms:

The SZC acts as an ion-exchanger, binding potassium in exchange for sodium and hydrogen. However, the released sodium can be absorbed; and the resulting volume expansion can cause congestive heart failure. Although, in adults with hyperkalaemia receiving SZC, no absorption and no clinically meaningful changes in serum sodium levels have been seen (remained within the normal range), in general, sodium retention leads to fluid accumulation in tissues (oedema), contributing to the symptoms of CCF, such as swelling in the legs, fluid in the lungs (pulmonary oedema), and abdominal swelling (ascites). Even with normal serum sodium, this fluid retention can worsen cardiac function by causing pulmonary congestion and increasing the workload on the heart (Abassi et al 2022).

Evidence source(s) and strength of evidence:

A pooled analysis of eight clinical trials was conducted to assess the potential risk of heart failure associated with treatment using SZC. Differences in cardiac failure were compared both on absolute scale, difference in Kaplan-Meier (KM) estimates, and relative scale, hazard ratio (HR). Initially the risk for cardiac failure was explored within the subgroups of prior/no-prior HF at baseline, then within subgroups of patients with prior heart failure at baseline. The analysis indicated an increased risk of worsening heart failure (HF) with SZC in patients with a history of heart failure was observed. However, the risk of new-onset heart failure remains unclear, but at this time there is no reasonable possibility of a causal relationship between SZC and new onset of heart failure. The analysis of de-novo CF cases indicates that SZC may have contributed to some instances to overall fluid overload, particularly at the higher 10g dose, but the presence of confounding factors, such as worsening renal function, uncontrolled hypertension, and lifestyle factors (e.g., alcohol use), complicates the assessment. The occurrence of edema before CF in a few cases raises the possibility that SZC might play a role in fluid retention, but these cases remain the minority.

Characterisation of the risk:

Clinical study data were divided in 3 pools; (1) placebo-controlled titrated dose studies, including Stabilize CKD, Realize-K, and Prioritize HF; (2) single-arm studies, consisting of ZS-005 and Japan-LTS; and (3) placebo-controlled fixed dose studies, which included ZS-004, Harmonize-Global, and Harmonize-Asia.

In Pool 1 [551 patients) on SZC and 544 on placebo (no prior HF: 331 in SZC and 335 in Placebo group]an increased absolute risk for SZC vs placebo within the subgroup of patients with prior-HF at baseline with no apparent increased in risk for HF observed in the non-HF population. The Kaplan-Meier difference in HF risk at 80 days in non-HF subjects in this pool was 0.7 (95% CI: -0.3, 1.6), with a hazard ratio (HR) of 5.8 (95% CI: 0.7, 48.1) and a p-value of 0.065. The limited size and length, and low incidence in non-HF population made conclusions for the new onset HF subgroup difficult and inconclusive. At this time there is no reasonable possibility of a causal relationship between SZC and new onset of heart failure.

However, an increased risk of heart failure worsening with SZC in patients with a history of heart failure was observed.

In Pool 2, involving 896 SZC-treated patients (with 766 subjects with no-prior HF), new onset HF events were reported in 22 patients (2.9%), with a Kaplan-Meier estimate of 3.2% at one year. The lack of specific data on recent HF history, including hospitalizations within the past 12 months, limited the assessment.

In Pool 3, SZC at doses of 5 g once daily (n=244) and 10 g once daily (n=250) was compared with placebo (n=185). Six HF events were observed, all in SZC-treated patients, with two of these cases having baseline HF. The small number of events in this pool restricted the ability to draw meaningful conclusions.

Overall, the data across all pools do not indicate a definitive increased risk of new onset HF with SZC but the possibility cannot be excluded. At this time there is no reasonable possibility of a causal relationship between SZC and new onset of heart failure. However, an increased risk of heart failure worsening with SZC in patients with a history of heart failure was observed.

Severity and reversibility

Moderate-to-severe heart failure has been observed in patients receiving sodium zirconium cyclosilicate (SZC). In most cases, SZC treatment was not discontinued due to the event. In the majority of instances, the heart failure resolved while patients continued SZC therapy. No cases with a fatal outcome have been reported.

Risk factors and risk groups

The risk of cardiac failure associated with SZC treatment is influenced by multiple factors and patient populations. Key risk factors include pre-existing cardiac conditions (e.g., coronary artery disease), renal impairment leading to sodium retention and fluid overload, and advanced age with reduced cardiac reserve. Sodium sensitivity, particularly in salt-sensitive hypertension or fluid balance disorders, also elevates risk. Concomitant use of fluid-retentive medications (e.g.,NSAIDs, corticosteroids, certain antihypertensives) further exacerbates this, especially in patients with comorbidities like diabetes, obesity, or CKD and adrenal insufficiency (Mladenka et al 2018, Gibbs et al 2000).

Preventability

Preventing new-onset cardiac failure associated with SZC is feasible through routine clinical management and monitoring. Monitoring for signs of fluid retention and regular cardiac assessments allows for timely therapeutic adjustments. The established clinical practices, such as the use of diuretics and optimization of comorbid conditions like hypertension or CKD, are

effective in mitigating risks. Importantly, there is no novel mechanism underlying this risk; such issues are well-recognized and manageable with standard clinical interventions (Triposkiadis et al 2024).

Impact on the risk-benefit balance of the product:

Cardiac failure is a chronic, progressive condition characterised by progression of breathlessness, tiredness, oedema and general feeling of weakness. Therefore, if undetected, or if appropriate intervention is not implemented, the benefit risk balance may be impacted.

Public health impact

As the impact is to the treated population only there is no public health impact.

2.7.3.2 Presentation of missing information

Not applicable.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Table 2-7 Summary of safety concerns

Important identified risks	None
Important potential risks	New Onset Cardiac Failure
Missing information	None

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for Cardiac Failure:

Adverse reaction (AE) follow-up questionnaires are in use to enhance follow-up information of reported events.

See Annex 4 for copies of AE follow-up questionnaires for spontaneous reports of cardiac failure.

Other forms of routine pharmacovigilance activities for New Onset Cardiac Failure:

None.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or on-going post-authorisation studies.

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

None.

5.2 ADDITIONAL RISK MINIMISATION MEASURES

None.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-1 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential Risk: New onset cardiac failure	None.	Routine pharmacovigilance beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous Reports.

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR LOKELMA (SODIUM ZIRCONIUM CYCLOSILICATE)

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

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

This summary of the RMP for LOKELMA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 LOKELMA's RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

LOKELMA is authorised for the treatment of hypokalaemia in adult patients. It contains sodium zirconium cyclosilicate as a powder, which is suspended in water and swallowed.

Further information about the evaluation of LOKELMA’s benefits can be found in LOKELMA’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/lokelma#:~:text=What%20is%20Lokelma%20and%20what,active%20substance%20sodium%20zirconium%20cyclosilicate.

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of LOKELMA together with measures to minimise such risks and the proposed studies for learning more about LOKELMA'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 (e.g. 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 so that immediate action may be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

6.2.1 List of important risks and missing information

Important risks of LOKELMA 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 LOKELMA. 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 (e.g. on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

Important identified risks	None
Important potential risks	New Onset Cardiac Failure
Missing Information	None

6.2.2 Summary of important risks

Important Potential Risk: New onset cardiac failure

Table 6-2 Important potential risk: New onset cardiac failure

Evidence for linking the risk to the medicine	A pooled analysis of eight clinical trials was conducted to assess the potential risk of heart failure associated with treatment using SZC. Due to variations in study designs, the analysis was divided into three distinct pools: (1) placebo-controlled titrated dose studies, including Stabilize CKD, Realize-K, and Prioritize HF; (2) single-arm studies, consisting of ZS-005 and Japan-LTS; and (3) placebo-controlled fixed dose studies, which included ZS-004, Harmonize-Global, and Harmonize-Asia. Difference in risk was compare both on absolute scale, difference in Kaplan-Meier (KM) estimates, and relative scale, hazard ratio (HR). Initially the risk for heart failure was explored within the subgroups of prior/no-prior HF at baseline, then within subgroups of patients with prior heart failure at baseline. The analysis suggested that the risk of new-onset heart failure remains unclear, but at this time there is no reasonable possibility of a causal relationship between SZC and new onset of heart failure. However, an increased risk of heart failure worsening with SZC in patients with a history of heart failure was observed.
Risk factors and risk groups	The risk of cardiac failure associated with SZC treatment is influenced by multiple factors and patient populations. Key risk factors include pre-existing cardiac conditions (e.g coronary artery disease), renal impairment leading to sodium retention and fluid overload, and advanced age with reduced cardiac reserve. Sodium sensitivity, particularly in salt-sensitive hypertension or fluid balance disorders, also elevates risk. Concomitant use of fluid-retentive medications (e.g., NSAIDs, corticosteroids, certain antihypertensives) further exacerbates this, especially in patients with comorbidities like diabetes, obesity, or CKD and adrenal insufficiency (Mladenka et al 2018,Gibbs et al 2000).
Risk minimisation measures	No risk minimisation measures

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

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

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for LOKELMA.

7 PART VII: ANNEXES

7.1 ANNEX 4: Specific adverse drug reaction follow-up forms

Cardiac Failure Adverse Event Report Questionnaire

Case ID: Date of Receipt:

Thank you for reporting an adverse event of/related to Cardiac Failure (CF) experienced by a patient under your care receiving Lokelma (SZC). To better understand and effectively characterise CF reports received from Lokelma patients, we require some further information to make a full assessment. Please could you provide responses to the following questions. Where appropriate, you may indicate if you have already provided the information, or if you do not have this information. Any additional data we receive is useful for us to preserve the safety of patients and provide the best information for prescribers to preserve safety of our patients.

Please provide severity (NYHA Classification) of cardiac failure (CF) at the time of adverse event, if applicable (Select one): _____

NYHA class I- No symptoms and no limitation in ordinary physical activity

NYHA class II- Mild symptoms and slight limitation during ordinary activity

NYHA class III- Marked limitation in activity due to symptoms, even during less-than ordinary activity. Comfortable only at rest

NYHA class IV- Severe limitations. Experiences symptoms even while at rest. No Prior Heart Failure, Unknown

If the patient has a history of cardiac failure, please check that this is recorded at Medical History.

At the time of the diagnosis of the CF event, did the patient present with any recent history of the following risk factors for cardiovascular (CV) disease:

Yes □ No □ (if yes please provide details/select all applicable)

History of CV disease (please select any/all that apply and provide start/stop dates [DD/MMM/YYY])	
□ Cardiac Failure Start date: _____ Stop date: _____ NYHA class: _____	□ Coronary artery disease with or without myocardial infarction Start date: _____ Stop date: _____

□ Oedema related events (Fluid retention, Generalised oedema, Hypervolaemia, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling) Specify: _____ Start date: _____ Stop date: _____	□ Prior use of potentially cardiotoxic therapy or radiotherapy to chest / mediastinum Specify: _____ Start date: _____ Stop date: _____
□ Pulmonary oedema Start date: _____ Stop date: _____	□ Current or previous myocarditis, pulmonary hypertension, and /or pulmonary embolism Specify: _____ Start date: _____ Stop date: _____
□Cardiovascular conditions (such as hypertensive heart disease with left ventricular hypertrophy, Pericardial disease, Valvular heart disease, Cardiomyopathy) Specify: _____ Start date: _____ Stop date: _____	□ Arrhythmia Specify the type: _____ Start date: _____ Stop date: _____
□Congenital heart disease Yes/No: _____	□Family history of premature CV disease (<50 years) Yes/No: _____
Other Condition: _____ Start date: _____ Stop date: _____ Other information: _____	Other Condition: _____ Start date: _____ Stop date: _____ Other information: _____

Other risk factors for CV disease (please select any/all that apply and provide start/stop dates [DD/MMM/YYY]):

□Diabetes Start date: _____ Stop date: _____	□Obesity Start date: _____ Stop date: _____	□ Hypertension Start date: _____ Stop date: _____
□Hyperlipidaemia Start date:_____ Stop date: _____	□Kidney dysfunction Start date: _____ Stop date: _____	□Smoking Start date: _____ Stop date: _____

☐High alcohol intake/alcohol abuse Start date: _____ Stop date: _____	Other Condition:_____ Start date: _____ Stop date: _____ Other info: _____	Other Condition: _____ Start date: _____ Stop date: _____ Other info: _____

Prior to and/or at the time of the diagnosis of the CF event, was the patient receiving concomitant treatment with any medications (other than Lokelma)?:

Yes ☐ No ☐ (if yes please provide details [below])

Medication Type	Medication Name	Dose (Please give units and regimen)	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
☐NSAIDs				
☐(Renin-angiotensin system) RAASI inhibitors (e.g. ACE inhibitors)				
☐Diabetes medications				
☐Blood pressure medications				
☐Diuretics				
☐Beta blockers				
☐Potentially cardiotoxic medicines (e.g. anthracyclines, HER2 inhibitors etc.)				
☐Any other medication relevant to the CF event				

Prior to and/or at the time of the diagnosis of the CF event, did the patient present with any of the following potential underlying cause(s):

Yes ☐ No ☐ (if yes please provide details/select all applicable)

Recent changes in blood pressure or change in blood pressure and/or heart failure medications	Yes ☐ No ☐ (if yes please provide details) Change in dosage: _____ Start date: _____ Stop date: _____ Other info: _____
Recent I.V. fluid challenge	Yes ☐ No ☐ (if yes please provide details) Change in dosage: _____ Start date: _____ Stop date: _____ Other info: _____
C – Acute Coronary Syndrome H – Hypertension Emergency A - Arrhythmia M – Acute Mechanical Cause P – Pulmonary Embolism	Yes ☐ No ☐ (if yes please provide details) Condition: _____ Start date: _____ Stop date: _____ Other info: _____

Symptoms of New or Worsening cardiac failure?

Symptoms (Please select all applicable)

☐ Dyspnoea ☐ Chest pain/discomfort ☐Palpitations ☐ Decreased Exercise Tolerance ☐ Fatigue
☐ Orthopnoea / Paroxysmal Nocturnal Dyspnoea ☐ Peripheral Oedema
☐ Altered Mental Status ☐ Other Symptoms of Heart Failure (Please specify below):

_____

Physical examination (Please select all applicable)

☐ Peripheral Oedema
☐ Pulmonary Rales/Crackles/Crepitations
☐ Increased Hepatojugular Reflux
☐ S3 Gallop
☐ Cool Extremities
Heart Rate _____(BPM)
Blood Pressure _____(mmHg)
Other Symptoms of Heart Failure _____

☐ Increased Abdominal Distension/Ascites
☐ Increased Jugular Venous Pressure
☐ Clinically Significant or Rapid weight gain
☐ Heart murmur (e.g. MR)

Body temp _____ºC/ºF (Please select units)
Oxygen saturation _____%

As part of the differential diagnosis, were any cardio-respiratory investigations conducted to confirm the CF event: Yes ☐ No ☐ Unknown ☐

(if yes please provide the details below and also the investigation results as an attachment to this completed questionnaire)

Diagnostic/Laboratory Tests

Please provide date(s) and results of the following relevant diagnostic/laboratory tests, if applicable.

Relevant Diagnostic/Laboratory Tests	Date(s) (dd/mm/yyyy)	Results
☐ Echocardiography (ECHO) / Radionuclide ventriculography (MUGA)		% LVEF:
☐ Chest X-ray		
☐ Cardiac magnetic resonance imaging (MRI) / positron emission tomography (PET)		
☐ Electrocardiography (ECG)		
☐ Troponin test		
☐ Natriuretic peptides (e.g. BNP, NT-proBNP)		
☐ Creatine kinase-muscle/brain (CK-MB)		
☐ Creatine kinase-muscle/brain (CK-MB)		
☐ Other(s)		

Were any laboratory test conducted to aid diagnosis or rule out an associated clinically significant abnormality (e.g. Blood counts [white cell count, haemoglobin level, haematocrit] and/or Liver Function Tests [ALT, AST, Bilirubin], and/or Renal function test [serum creatinine, BUN, serum electrolytes, serum +/- urinary albumin (considering nephrotic syndrome)] and/or thyroid function tests)?

Yes ☐ No ☐ Unknown ☐

(if yes please provide the investigation results as an attachment to this completed questionnaire)

OUTCOME OF THE CARDIAC EVENT (please select only ONE):

☐ Ongoing
☐ Fatal
☐ Recovering
☐ Recovered (Date of resolution ____/_____/_____)
☐ Recovered with sequalae (Date of resolution ____/_____/_____)
☐ Unknown

ACTION TAKEN WITH LOKELMA FOR THE EVENT:

Lokelma Start date: Action taken:

☐ None ☐ Dose reduced ☐ Permanently discontinued (Date of last dose: ___/____/_____) If discontinued, did the event recover/improve? Yes ☐ No ☐ ☐ Temporary stop (Stop date: ___/____/_____Re-Start date: ___/____/_____) Did the event recover/improve upon withdrawal of Lokelma? Yes ☐ No ☐ Did the event re-occur upon re-start of Loklema? Yes ☐ No ☐
Any treatment was given to the patient for the reported event? Please specify below
_____ _____ _____ _____ _____ _____

Please complete the below section if the reported cardiac event was fatal:

Was an autopsy performed?	Yes ☐ No ☐
If yes, please provide the results and/or attach a copy of the autopsy report.	_____ _____ _____ _____ _____ _____

Reporter's Signature: _____ Date: _____

Free text space for any additional details relevant to the cardiac failure event not captured above.

_____
_____
_____

7.2 ANNEX 6: Details of proposed additional risk minimisation activities

None.

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