EU Risk Management Plan for Joenja®
(leniolisib)

RMP version to be assessed as part of this application:

RMP version number:	1.0
Data lock point for this RMP:	23 Sep 2025
Date of final sign-off:	26 Mar 2026

Rationale for submitting an updated RMP:

On request of CHMP

Summary of significant changes in this RMP:

Not applicable as this is the initial marketing authorisation application submission

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number:	1.0
Approved with procedure:	EMEA/H/C/005927
Date of approval (opinion date):	26 Mar 2026

QPPV name:	Delphine Bertram
QPPV signature:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is appended at the end of this document.

TABLE OF CONTENT

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
Akt	Protein kinase B
ALT	Alanine amino-transferase
APDS	Activated PI3Kδ syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
CVID	Common Variable Immune Deficiency
DLP	Data Lock Point
DSUR	Development Safety Update Report
EAP	Expanded access programs
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ESID	European Society of Immune Deficiencies
EU	European Union
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
FL	Follicular lymphoma
GI	Gastrointestinal
GLP	Good Laboratory Practice
GVHD	Chronic Graft Versus Host Disease
hERG	human ether-à-go-go related gene
HI	Hepatic impairment
HIGM	Hyper IgM Syndrome
HLT	High Level Term
HSCT	Haematopoietic Stem Cell Transplantation
ICH	International Council for Harmonization
IEI	Inborn Error of Immunity
IRT	Immunoglobulin Replacement Therapy
NOAEL	No Observed Adverse Effect Level
NTI	Narrow Therapeutic Index
OLE	Open-label extension
PASLI	p110δ- activating mutation causing senescent T-cell, lymphadenopathy and immunodeficiency
pAkt	Phosphorylated protein kinase B
PI3K(δ)	Phosphoinositide 3-kinase (delta)
PID	Primary Immunodeficiency Disorder
PIP3	phosphatidylinositol-3,4,5-trisphosphate
PJP	Pneumocystis Jirovecii Pneumonia
PK	Pharmacokinetics
PL	Package leaflet
PSS	Primary Sjögren's syndrome
PSUR	Periodic Safety Update Report
PT	Preferred term
QOL	Quality of life
ROW	Rest of world

SCAR	Severe cutaneous adverse reactions
SD	Standard Deviation
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA Query
SOC	System organ class
TEN	Toxic Epidermal Necrolysis
UK	United Kingdom
ULN	Upper Limit of Normal

PART I: PRODUCT OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Leniolisib
Pharmacotherapeutic group(s) (ATC code)	L03AX22
Marketing Authorization Applicant	Pharming Technologies B.V.
Medicinal products to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	Joenja
Marketing authorization procedure	Centralised, orphan drug
Brief description of the product	*Chemical class* Protein kinase inhibitor
	Summary of mode of action Inhibition of phosphoinositide 3-kinase delta (PI3Kδ)
	Important information about its composition Contains lactose monohydrate
Hyperlink to the Product Information	The Product Information can be found in Module 1.3.1
Indication(s) in the EEA	*Current:* Treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	*Current:* The recommended dose in adult and adolescent patients who weigh more than 45 kg is 70 mg leniolisib twice daily approximately 12 hours apart.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	*Current (if applicable):* Film-coated tablet, 70 mg
	Proposed (if applicable): Not applicable.
Is the product subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

Leniolisib is indicated for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more.

Genetics of the disease

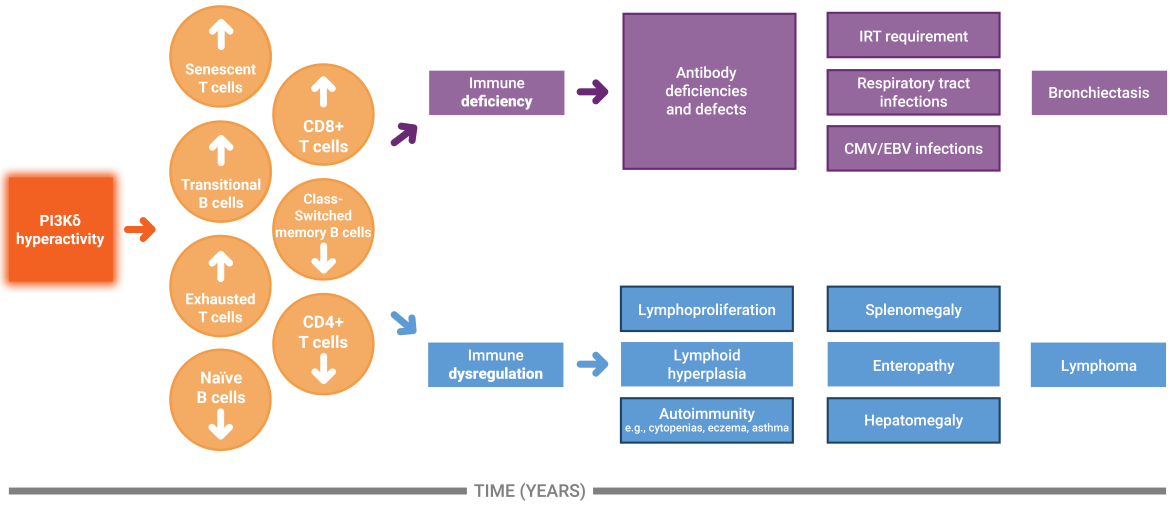
APDS is a rare heterozygous autosomal dominant inborn error of immunity (IEI) caused by a mutation in either the PIK3CD or PIK3R1 genes coding for the catalytic and regulatory domains of the PI3K dimer, respectively. APDS is a recently identified disease that was identified in 2006 (Jou, 2006) and fully described in 2013 (Angulo, 2013). These activating mutations increase activity of PI3Kδ, a promoter of activity in the immune system. Activated PI3Kδ syndrome has also been referred to as p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency. The diagnosis of APDS is made by sequencing the genes PIK3CD (APDS1) or PIK3R1 (APDS2) in patients with a compatible phenotype, i.e., immunodeficiency and lymphoproliferation of unknown origin, or a relevant family history.

Phenotypic crossover can make it difficult to distinguish from other IEI and differences in case-finding strategies have made phenotype frequency reporting and comparison a challenge (Coulter, 2017). The similarity in presentation of APDS with IEI illustrates the difficulty in identifying APDS from presentation alone and why some patients are first misdiagnosed with IEI. Genetic testing for the mutation in the PIK3CD or PIK3R1 genes which leads to APDS is a definitive method of differentiation of the underlying cause of this phenotypically complex disease.

Pathophysiology

PI3Kδ hyperactivity results in dysregulation of T cells and B cells and cause at the one hand immune deficiency presenting as antibody deficiencies and defects and a clinical picture of respiratory tract infections and cytomegalovirus (CMV) / Epstein-Barr virus (EBV) infections and a long-term effect of bronchiectasis. On the other hand, it causes immune dysregulation, leading to lymphoproliferation, lymphoid hyperplasia and autoimmunity and presenting as splenomegaly, enteropathy, hepatomegaly and over time as lymphoma. Figure 1 visualises the APDS disease pathway.

Figure 1 APDS disease pathway



CD, cluster of differentiation; CMV, cytomegalovirus; EBV, Epstein-Barr virus; IRT: immunoglobulin replacement therapy.

Based on the mechanism of action of PI3Kδ inhibition, leniolisib corrects the PI3Kδ hyperactivity present in patients with APDS1 and APDS2.

This means that short-term beneficial effects of leniolisib are correction of immunophenotype as measured by the normalization of dysregulated T cells and B cells and reduced lymphoproliferation as measured by reduction in index lesion volume. Reduction in lymphoproliferation and correction of immunophenotype are two clinically monitored hallmarks of the disease improving. These early beneficial effects will result in time in correction of the immune deficiency and immune dysregulation. Clinical trials have shown that a decrease in infections over time starts in the first year, but the number of infections continues to decrease in the second, third and even subsequent years. In parallel, gradual reductions in the dose of intravenous immunoglobulin replacement therapy were seen. The correction of immune dysregulation translates in a decrease in lymphoproliferation and can already be shown within the first 12 weeks of treatment (and was therefore selected as primary endpoint in the study), but reductions in autoimmunity and lymphoma are long-term effects and can be seen only at long-term follow-up.

Frequent signs and symptoms

Signs and symptoms of the disease are not limited to infections, but APDS can affect all organs systems. Frequent signs and symptoms are listed in Table SI.1 below.

Table SI.1: Frequent signs and symptoms of APDS

Parameters	Total	APDS1	APDS2	P value
Pneumonia (%)	106 (43.6)	66 (36.9)	40 (62.5)	<0.001*
Otitis (%)	70 (28.8)	53 (29.6)	17 (26.6)	0.644
Sinusitis (%)	63 (25.9)	53 (29.6)	10 (15.6)	0.028*
Meningitis (%)	6 (2.5)	6 (3.4)	0.0	0.345
Diarrhoea (%)	39 (16)	27 (15.1)	12 (18.8)	0.493
Bronchiectasis (%)	69 (28.4)	61 (34.1)	8 (12.5)	0.001*
Abscess (%)	13 (5.3)	12 (6.7)	1 (1.6)	0.193
Septicaemia (%)	13 (5.3)	10 (5.6)	3 (4.7)	1.0
Fungal infection (%)	21 (8.6)	17 (9.5)	4 (6.3)	0.427
Enteropathy (%)	65 (26.7)	51 (28.5)	14 (21.9)	0.305
Arthritis (%)	4 (1.6)	3 (1.7)	1 (1.6)	1.0
Autoimmunity (%)	69 (28.4)	56 (31.3)	13 (20.3)	0.095
Lymphadenopathy (%)	149 (61.3)	100 (55.9)	49 (76.6)	0.004*
Splenomegaly (%)	115 (47.3)	90 (50.3)	25 (39.1)	0.123
Hepatomegaly (%)	70 (28.8)	62 (34.6)	8 (12.5)	0.001*
Failure to thrive (%)	50 (20.6)	17 (9.5)	33 (51.6)	<0.001*
Endocrinopathies (%)	13 (5.3)	11 (6.1)	2 (3.1)	0.523
Granulomatous lesions (%)	4 (1.6)	3 (1.7)	1 (1.6)	1.0
Malignancy (%)	31 (12.8)	19 (10.6)	12 (18.8)	0.094
Allergy and asthma (%)	15 (6.2)	14 (7.8)	1 (1.6)	0.125
Eye infection (%)	26 (10.7)	13 (7.3)	13 (20.3)	0.004*
Neurologic abnormality (%)	34 (14)	17 (9.5)	17 (26.6)	0.001*
ENT problem (%)	86 (35.7)	62 (34.8)	24 (38.1)	0.642
Hepatobiliary disorders (%)	17 (7)	13 (7.3)	4 (6.3)	1.0
Orthopaedic abnormalities (%)	15 (6.2)	8 (4.5)	7 (10.9)	0.075

Table SI.1: Frequent signs and symptoms of APDS

Parameters	Total	APDS1	APDS2	P value
Dental problem (%)	10 (4.1)	7 (3.9)	3 (4.7)	0.726
BCGosis (%)	4 (1.6)	2 (1.1)	2 (3.1)	0.284

*P value is statistically significant <0.05.
APDS, activated phosphoinositide 3-kinase delta syndrome; BCGosis, disseminated infection with bacillus Calmette-Guerin; ENT, ear, nose, and throat.
Source: Jamee, 2020.

Incidence

The world-wide APDS incidence rate is estimated to be 1 to 2 per million people. Since APDS is an inborn error of immunity, the incidence rate is expected to be 1 to 2 per million births.

In 2021, 4.09 million babies were born in the EU, which theoretically means 4-8 babies with APDS (Eurostat, 2023).

Prevalence

On 19 October 2020, orphan designation EU/3/20/2339 was granted by the European Commission to Pharming Group N.V., the Netherlands, for leniolisib for the treatment of APDS. At the time of designation, APDS affected approximately 1 in 1,000,000 people in the European Union (EU). This was equivalent to a total of around 500 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the Committee for Orphan Medicinal Products (EU/3/20/2339: Orphan designation for the treatment of APDS).

The genetic cause of APDS was first described in 2006 (Jou, 2006) but was only fully characterized in 2013 (Angulo, 2013 and Lucas, 2016). In a recent study of 886 index cases of primary immune deficiency, only 4 patients were found with APDS mutations (Thaventhiran, 2020). The largest systematic review to date identified a total of 243 APDS cases in the published literature (Jamee, 2020). The prevalence rate cited in the literature is 1-2/million (Coulter, 2018). To date, no formal epidemiological database is available to accurately estimate the prevalence of APDS.

Prevalence rates of this autosomal dominant disease can be estimated by adjusting prevalence rates of Common Variable Immune Deficiency (CVID) in the published literature:

Eighty-two percent (82%) of patients with APDS have a Hyper IgM Syndrome (HIGM) (Angulo, 2013). Thus, the prevalence of APDS can be estimated based on the prevalence of HIGM.

- 0.083% of the population has a primary immunodeficiency (Boyle and Buckley, 2007). While this percentage includes only the diagnosed cases, it is likely to include most symptomatic patients.
- 2.4% of patients with a primary immunodeficiency have HIGM of unknown cause (Eades-Perner, 2007).
- 20% of patients with HIGM of unknown cause have been found in genetic screening efforts to have APDS (Angulo, 2013).
- Multiplying these frequencies provides the estimated frequency of APDS with HIGM in the general population. A correction is added for the additional 18% of patients with APDS without HIGM (Angulo, 2013).
- Applying the final frequency to a reference population in the EU, Iceland, Lichtenstein, Norway, and the UK of approximately 519,200,000 (Eurostat 2023) results in a relative prevalence of approximately up to 4.7 per million and a probable minimum absolute

prevalence of approximately 2,440 patients with APDS in the EU, Iceland, Lichtenstein, Norway, and the UK.

- No corrections for other epidemiologic population characteristics that change the likelihood of having APDS.

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

As of 2024, APDS is one of over 559 identified inborn errors of immunity (IEI) (Bousfiha et al, 2025). There are no known risk factors for the development of APDS outside of a relevant family history for autosomal dominant transmission of the mutation. The gender make-up of the APDS population in a review of the largest published APDS population of 243 patients is 123/243 (50.6%) male, 87/243 (35.8%) female, and 33/243 (13.6%) unknown (Jamee, 2020).

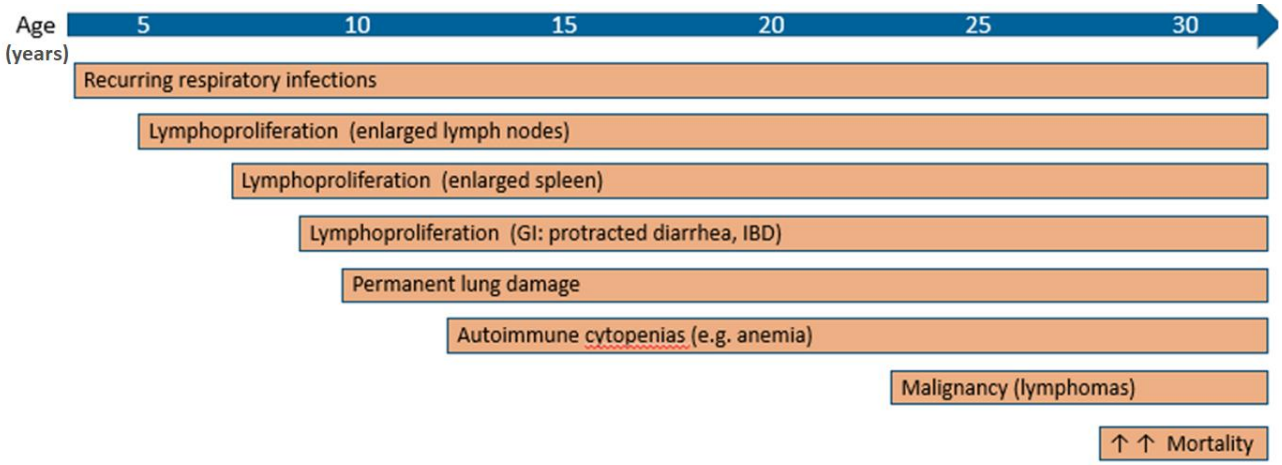
In the completed sponsor-initiated randomised, placebo-controlled trial of patients with APDS treated with leniolisib for 12 weeks, the patients had the following characteristics: 15/31 (48.4%) male, 16/31 (51.6%) female, 25/31 (80.6%) Caucasian, 2/31 (6.5%) Asian, 2/31 (6.5%) Black, 2/31 (6.5%) Other, 1/31 (3.2%) Hispanic/Latino, 21/31 (67.7%) Not Hispanic/Latino, and 9/31 (29.0%) Ethnicity not reported (clinical study report (CSR) CCDZ173X2201 Part 2, 2022 and Rao, 2023). The demographic characteristics of the patients in the company sponsored trial are generally reflective of those for the APDS population reported in the published literature.

Outcome of the untreated disease

Signs and symptoms of APDS start with recurring respiratory infections, but with time, other organ systems become involved as well. Jamee provided an overview of APDS-related signs and symptoms in a cohort of 243 patients (Jamee, 2020; see Table SI.1 above).

Figure 2 provides a chronological overview of the symptoms associated with patients with APDS will develop.

Figure 2: Chronological overview of the symptoms associated with APDS.



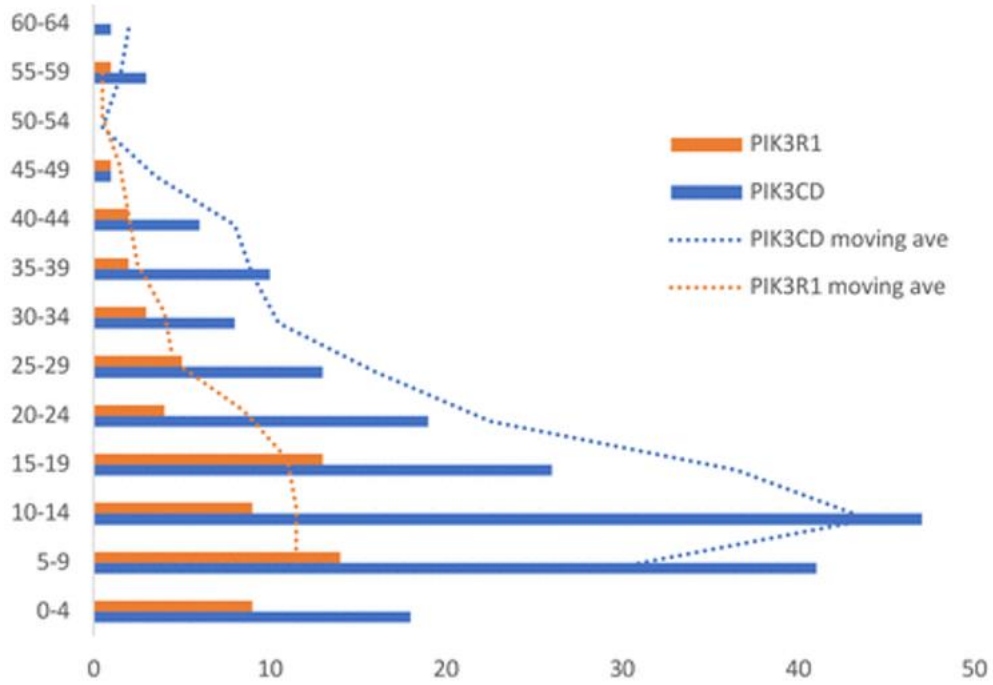
GI, gastrointestinal; IBD, inflammatory bowel disease.

Hanson and Bonnen have published real-world evidence of mortality and survival rates in APDS. She conducted a review of the medical literature and identified 256 individuals who had a molecular diagnosis for APDS as well as age at last report: 193 individuals with APDS1 and 63 with APDS2. A Kaplan-Meier survival analysis for APDS showed the conditional survival rate at the age of 20 was 87%, age 30 was 74%, age 40 and 50 were 68%. Review of causes of death showed that the most common cause of death was lymphoma, followed by complications from haematopoietic stem cell transplantation (HSCT). The mortality data suggests

that the standard of care treatment for APDS, immunoglobulin replacement therapy, appears to prevent most deaths due to severe infection, however, new treatments are needed to mitigate the risk of death from lymphoma and other cancers (Hanson and Bonnen, 2024).

The median age of individuals reported with APDS1 was 13 years with an average of 17 years (range, 1 – 64 years). The median age of individuals reported with APDS2 was 14 years with an average of 16 years (range, 1 – 56 years). The age distribution was significantly different between the two groups due to there being disproportionately more individuals with APDS1 in the 5 - 15 years age range (p = 3.6E-10) (Figure 3). Gender was not available for all individuals in the study. For APDS1, 103/182 (57%) individuals were reported as being male and 79/182 (43%) individuals were noted to be female. For APDS2, 20/39 (51%) individuals were reported as being male with 19/39 (49%) individuals were noted to be female (Hanson and Bonnen, 2024).

Figure 3: Age (in years) at last report in a cohort of 256 individuals with APDS.

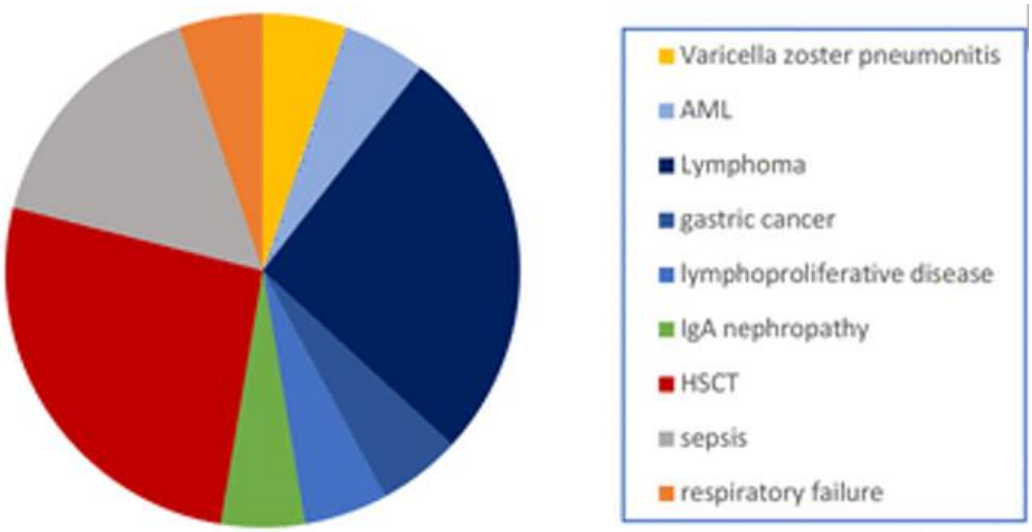


Note: The age at last report was plotted in 5-year age bins for individuals with a molecular diagnosis of pathogenic PI3KCD resulting in APDS1 (orange chart), and for those with a molecular diagnosis of pathogenic PI3KR1 (blue chart). The moving average of the age at last report was plotted for individuals with APDS1. PI3KD in blue (dotted line) and for individuals with APDS2/PI3KR1 in orange (dotted line).

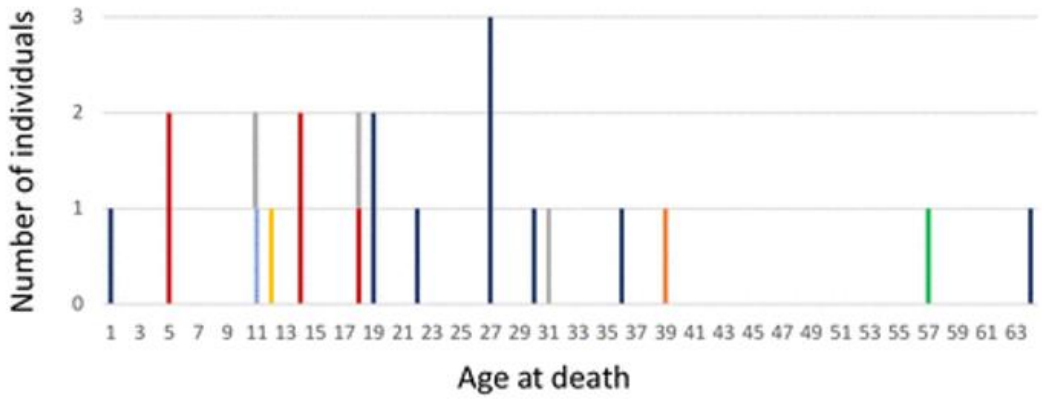
Twenty-four individuals with APDS1 in the Hanson and Bonnen, 2024 study were reported as being deceased. Age of death ranged from 1 – 64 years. The most common cause of death was tied between lymphoma (N = 5) and HSCT (N = 5) (Figure 4). The range of ages for death by lymphoma was 1 – 27 years, while the range of ages for death by HSCT was 5 – 18 years. The next most common cause of death was sepsis with no further information specified (N = 3, age range 11 – 31 years). Additional causes of death included: Varicella zoster pneumonitis (N = 1, age 12); Acute myeloid leukaemia (N = 1, age 22); lymphoproliferative disease (N = 1, age 11); gastric cancer (N = 1, age 64); IgA nephropathy (N = 1, age 57); respiratory failure (N = 1, age 39) (Figure 4) (Hanson and Bonnen, 2024).

Figure 4: Cause of death (A) and corresponding age (B) for APDS.

A)



B)



Note: A) Causes of death in individuals with APDS1 are shown and the size of the pie slice reflects the number of individuals with that cause of death. All individuals with APDS2 had the same cause of death, lymphoma, so it was not plotted. B) Cause of death in individuals with APDS1 and APDS2 was plotted with age of death (in years) on the x-axis and number of individuals plotted on the y-axis. The colour scheme in A) and B) is the same, with each colour indicating a different cause of death. The key for colour to cause of death is shown in the figure.
AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell transplantation; IgA, immunoglobulin A.

Five out of the 63 individuals with APDS2 in this study were reported as having died. Age of death ranged from 12 – 36 years. The cause of death was reported for 4/5 individuals who died with APDS2 and all four of their deaths were attributed to lymphoma (Hanson and Bonnen, 2024).

The main existing treatment options

Joenja (leniolisib) 70 mg film-coated tablets have been approved for marketing in the US by the FDA on 24-Mar-2023 for the treatment in APDS in adults and adolescents aged 12 years and older.

Existing treatment options in the EEA for the management of APDS are predominantly supportive such as immunoglobulin replacement therapy, antibiotics, antiviral agents, immunosuppressive agents (e.g., steroids, azathioprine, mycophenolate), splenectomy, rituximab, and sirolimus (rapamycin). The only exception is

HSCT which is potentially curative.

Antimicrobial prophylaxis: In cohort studies, approximately 60% of patients received antibiotic prophylaxis, although this alone was insufficient for most patients as they required supplemental immunoglobulin replacement therapy (IRT) for prevention of infections (Coulter, 2018). Despite an association with persistent, severe or recurrent herpesvirus infections, few patients were on long-term antiviral therapy (6%) (Coulter, 2018).

Immunoglobulin replacement therapy: Given the presentation of antibody deficiency with recurrent respiratory tract infections, many patients with APDS have been treated with long-term immunoglobulin replacement therapy (approximately 88%) (Coulter, 2018). While this has been reported to be beneficial in reducing respiratory tract infections, it does not prevent the development of herpesvirus infections nor lymphoproliferative or auto-immune complications.

HSCT: Allogenic HSCT has been described in 33 patients with significant pre-HSCT morbidity. Data suggests HSCT can be curative with a similar level of survival reported with HSCT in other primary immune deficiency disorders (PIDs) (around 80%). Jamee reported HSCT in 12.8% of patients with APDS, with a mortality risk of HSCT of 10-20% and acute or chronic graft versus host disease (GVHD) in 45% of transplanted patients with APDS. Maccari reports that 29/168 patients in the European Society of Immune Deficiencies (ESID) registry (17%) have received HSCT, at an age between 5 and 51 years, median 13.5 years (Maccari, 2023; Jamee, 2020; Coulter, 2018; Okano, 2019; Nademi, 2017).

Immunosuppression: Around 34% of patients with APDS present with inflammatory disease (Coulter, 2018). Autoimmune cytopenias have been reported to be responsive to steroids, rituximab and splenectomy, although rituximab treatment can be complicated by sustained B-cell lymphopenia (Coulter, 2018).

Sirolimus (also known as rapamycin): Due to its role downstream of PI3K, the mTOR inhibitor has been trialed in patients with APDS and was shown to have a benefit in the treatment of non-neoplastic lymphoproliferative disease in around 65% of patients. However, adverse events and limited effect on gastrointestinal disease and cytopenias remain an unmet need with this treatment approach (Coulter, 2018; Tangye, 2019). Sirolimus is not an approved therapy for APDS, globally.

There are currently a number of molecules that have the potential to compete in the APDS treatment landscape, although none are approved for the indication of APDS, including the first clinically tested PI3Kδ inhibitor idelalisib. Other PI3K inhibitors such as copanlisib and duvelisib are approved for the treatment of chronic lymphocytic leukaemia (CLL) and follicular lymphoma (FL), as are those currently under assessment (gedatolisib, buparlisib, dactolisib, apitolisib, pictilisib, or alpelisib). Idelalisib was also investigated in patients with APDS, but development was discontinued because of moderate efficacy and AEs that led to treatment discontinuation (Rao, 2023; Diaz, 2020; Helmer, 2017). The PI3K inhibitors used in oncology have all significant treatment-limiting serious adverse effects that impede their clinical development such as immune-related toxicities (primarily hepatotoxicities), pneumocystis pneumonia and other forms of pneumonitis, as well as colitis with severe diarrhoea (Smolewski, 2020). Leniolisib was specifically developed to offer selectivity for the PI3Kδ isoform over other PI3K isoforms thought to be related to off-target toxicity (Hoegenauer, 2017) and is the only molecule approved for the treatment of APDS to date (Joenja US PI).

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

An extensive non-clinical toxicology program consisting of *in vitro* and animal studies with leniolisib, tailored to the proposed route of administration (oral) and dose regimen (daily dosing) in the clinic was performed. This program, designed according to the International Council for Harmonization (ICH) M3 guideline as well as all other relevant ICH guidelines on safety, included pivotal general toxicity studies in rats (up to 26 weeks dosing) and cynomolgus monkeys (up to 39 weeks dosing), carcinogenicity study in mice, safety pharmacology studies in rats and monkeys, the standard battery of in vitro and in vivo genotoxicity studies, embryo-foetal developmental toxicity studies in rats and rabbits, a pre- and postnatal development as well as a 10-week juvenile toxicity study in rats, local tolerance test in rabbits, phototoxicity testing, a mechanistic in vitro study on the thyroid liabilities, and studies for impurities. All pivotal studies were performed in compliance with Good Laboratory Practice (GLP) and current accepted guidelines in terms of duration, animal numbers, and dose levels used.

Table SII.1 summarises the key potential safety concerns as addressed in the non-clinical studies and provides an evaluation of the relevance of the results of these studies for the usage of Joenja in a clinical setting.

Table SII.1: Safety concerns from non-clinical studies and human relevance

Key safety findings	Relevance to human usage
Toxicity: Acute or repeat-dose toxicity studies Immunosuppression: increase in opportunistic skin infections (rats, also with chronic dosing at 120 mg/kg/day) and gastrointestinal (GI) toxicity (i.e., inflammation/ infections (mice and monkeys) leading to severe diarrhoea (monkeys) exacerbated by the pharmacological effect of leniolisib.	In the completed clinical studies with leniolisib, no notable differences in skin infections and gastrointestinal related adverse events in the leniolisib versus the placebo treated participants were identified.
Toxicity: Teratogenicity/reproductive/juvenile toxicity Teratogenic in animals; embryonic and foetal development studies in rats and rabbits showed in rats only anophthalmia and in rats and rabbits microphthalmia and reduced orbital socket size at the highest dose levels (i.e., 120 and 100 mg/kg/day, respectively). Aglossia was reported in rabbits from 30 mg/kg/day. Leniolisib was detected in milk of lactating rats with concentrations increasing in a dose-dependent manner. Slight effects seen on the male reproductive organs (histopathological changes and reduced sperm production, in rats only) at high dose levels (≥120 mg/kg/day) were partially to fully reversible within a 4-week recovery period. A juvenile toxicity study in rats revealed an increase in mortality up to weaning (at 90 mg/kg/day) and pharmacologically related effects on lymphoid tissues and immunomodulation. Slight effects on male reproductive organs were noted (≥40 mg/kg/day), which did not translate into reduced fertility indices or pregnancy rates. In the pre- and postnatal developmental rat study, adverse effects on the progeny during the preweaning period, manifested as reduced pup survival and persistently lower pup weight during postweaning, were seen at maternal doses of 90 mg/kg/day.	Joenja may cause foetal harm in pregnant women. It is unknown whether Joenja and its metabolites are excreted in human milk. A risk to breastfed newborns / infants cannot be excluded. Breast feeding should be discontinued during treatment with Joenja. Reduced male fertility is not considered an important risk in humans. However, an effect cannot be ruled out. Joenja should not be used in infants younger than 1 year old.

Table SII.1: Safety concerns from non-clinical studies and human relevance

Key safety findings	Relevance to human usage
Toxicity: Carcinogenicity Leniolisib was not mutagenic nor clastogenic in *in vitro* and *in vivo* genotoxicity studies. Leniolisib was considered non-carcinogenic in the pivotal 26-week carcinogenicity study in transgenic CB6F1-Tg rasH2 hemizygous mice. Results from the pivotal 2-year rat carcinogenicity study will be delivered post marketing authorisation.	Immunosuppression related lymphomas cannot be excluded on the basis of the mechanism of action of leniolisib.
Safety pharmacology: Cardiovascular system, including potential effect on the QT interval In safety pharmacology studies, leniolisib was shown to inhibit the human ether-à-go-go related gene (hERG) channel with an IC_{50} value of 11.9 µM (5.4 µg/mL). The hERG IC_{50} is 26-fold higher than the $C_{max,\,u}$ at steady state in humans dosed at the therapeutic dose (70mg, BID). No effects on the nervous system and respiratory function were observed in the rat. Leniolisib caused QTc prolongation (mean of 13%; 32 ms above baseline) in the telemetry study in monkeys after a single dose of 150 mg/kg. Exposure in monkeys dosed at 150 mg/kg, corresponded to ~ 9-fold C_{max} and 6-fold $AUC_{0\text{-}24h,ss,\,u}$ of the human steady state exposure at the therapeutic dose. In monkeys dosed at 40 mg/kg/day for at least 25 weeks, a trend in QT/QTc prolongation was observed, the exposure ($AUC_{0\text{-}24h,\,u}$) was 2.3-fold the human therapeutic exposure at steady state.	In clinical studies, there were no significant changes in electrocardiogram (ECG) or vital signs and no evident relationship between leniolisib exposure and placebo adjusted QTcF change from baseline (data pooled from single dose ≤400 mg and multiple doses ≤140 mg BID).
Other toxicity-related information or data N/A	N/A

Conclusions on non-clinical data and relevance to human data

The main safety risks identified in the repeat dose toxicity studies were effects in the haemolymphopoietic system and the gastrointestinal tract. These were related to the pharmacological immunomodulatory properties of leniolisib resulting in opportunistic infections but were not observed in the clinic. Leniolisib is considered to be teratogenic in animals and it may cause foetal harm in pregnant women (not investigated). Leniolisib was found in rat milk, as it is unknown whether it is excreted in human milk; breast feeding should be discontinued during treatment with leniolisib. Leniolisib should not be used in infants younger than 1 year old. Slight effects in male reproductive organs (rats only) did not result in reduced fertility indices or pregnancy rates and is not considered an important risk in humans. One out of two carcinogenicity studies has been completed. Leniolisib was not carcinogenic, nor mutagenic or clastogenic in in vitro and in vivo genotoxicity studies. In monkeys, QTc prolongation was observed at a high single dose and a trend in QT/QTc prolongation was observed at ≥ 40 mg/kg/day dosed for at least 25 weeks. In clinical studies, there were no significant changes in ECG (including QTI interval evaluation) or vital signs.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

The proposed indication for Joenja in the EU is the treatment of APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more.

Table SIII.1 below reflects subject exposure in the ongoing and completed studies per data lock point (DLP) of this risk management plan (RMP) (23-Sep-2025).

Study CCDZ173X2201E1 – the open-label extension (OLE) of study CCDZ173X2201 was initiated in 2016 and terminated for non-safety related reasons on 30 January 2025 - last patient last visit. The final CSR was completed and final data have been included in the RMP.

Overall, 329 healthy volunteers and 129 subjects have been enrolled into the leniolisib clinical development program, of which 259 healthy volunteers (253 on leniolisib and 6 on ^{14}C-leniolisib) and 118 subjects have received treatment with leniolisib since the developmental international birth date of 20-Jul-2012. Out of 118 subjects dosed with leniolisib in clinical trials, 78 were subjects with APDS, 20 were subjects with pSS, 10 were subjects with PID and 10 were subjects with CVID. Estimates of overall cumulative subject exposure are provided in Table SIII.1 based upon completed and ongoing trials.

Table SIII.1: Estimated cumulative subject exposure to leniolisib in ongoing and completed clinical trials

Population	Treatment	Exposure from completed studies[a]	Estimated exposure from ongoing studies [c]	Total
Healthy volunteers	Leniolisib	226	27	253
	^{14}C-leniolisib	6	0	6
	Placebo	70	0	70
Subjects with pSS	Leniolisib	20	0	20
	Placebo	10	0	10
Subjects with APDS	Leniolisib	38	40	78[b]
	Placebo	10[d]	NA	10
Subjects with PID	Leniolisib	0	10	10
Subjects with CVID	Leniolisib	0	10	10

NA: Not applicable; pSS: Primary Sjögren's syndrome; PID: primary immunodeficiency disorder; CVID: common variable immunodeficiency disorder.

Definitions: Completed study: final clinical study report is available. Ongoing study: study was approved; study has begun but is currently on hold; study is terminated or completed (last patient last visit) but final clinical study report is not yet available.

[a]Data from completed studies up to 23-Sep-2025

Completed clinical studies include: CCDZ173X2101, CCDZ173X2102, CCDZ173X2104, CCDZ173X2203, CCDZ173X2201, CCDZ173X2201E1, LE 1101, LE 1102, LE 2101 and LE 5101.

[b]Some subjects may be counted twice for multiple treatments in cross-over designs studies.

[c]Data from ongoing studies: in healthy volunteers - LE 6101 (n=27), in APDS - CCDZ173X2201E1 (n=37), LE 3301 (n=21), LE 3302 (n=16), LE 4301 (n=3), in PID – LE 7201 (n=10, of which 7 rolled over to LE 7X01) , in CVID – LE 8201 (n=10).

[d] Note, 9 of the 10 subjects who received placebo, received leniolisib in the OLE-study (CCDZ173X2201E1). These 9 subjects are included in the 38 subjects treated with leniolisib.

Table SIII.2: Cumulative duration of exposure to leniolisib (person time)

Population	Duration of exposure	Number of Subjects[a]	Person time (months)
Healthy volunteers	<6 Months	232	86.7
	≥6 Months to <12 Months	0	0
	≥12 Months	0	0
Subjects all indications	1 to ≤12 weeks	21	56.3
	>12 weeks to ≤6 months	2	8.5
	6 months to ≤1 year	7	77.5
	1 to ≤2 years	20	320.8
	2 to ≤4 years	10	355.3
	>4 years	22	1406.2
Subjects with APDS	1 to ≤12 weeks	1	2.7
	>12 weeks to ≤6 months	2	8.5
	6 months to ≤1 year	7	77.5
	1 to ≤2 years	20	320.8
	2 to ≤4 years	10	355.3
	>4 years	22	1406.2
Total person time			**2311.6**

[a] Data up to 23-Sep-2025.
Completed studies include: CCDZ173X2101, CCDZ173X2102, CCDZ173X2104, CCDZ173X2203, CCDZ173X2201, CCDZ173X2201E1, LE 1101, LE 1102, LE 2101 and LE 5101.
Ongoing studies with interim CSR (exposure as in interim CSR) available: LE 3301 (n=21), LE 4301 (n=3).

Table SIII.3: Exposure per age group and gender

Age group / Gender	Patients		Leniolisib/Placebo	
	Male[a]	Female[a]	Male[a]	Female[a]
Subjects all indications				
Infants (0 to 11 months)	0	0	0	0
Infants, toddlers, children (1-3 years)	0	0	0	0
Children (4 to 11 years)	15	6	15/0	6/0
Adolescents (12 to 17 years)	7	7	7/0	7/0
Adults (18 to 64 years)	19	35	18/1	26/10
65-74 years	1	3	1/0	2/0
75-84 years	0	0	0	0
85 + years	0	0	0	0
Total	42	51	41/1	41/10
Subjects with APDS				
Infants (0 to 11 months)	0	0	0	0
Infants, toddlers, children (1-3 years)	0	0	0	0
Children (4 to 11 years)	15	6	15/0	6/0
Adolescents (12 to 17 years)	7	7	7/0	7/0
Adults (18 to 64 years)	16	12	16/0	11/1
65-74 years	0	0	0	0
75-84 years	0	0	0	0
85 + years	0	0	0	0
Total	38	25	38/0	24/1

Note: If patients received both leniolisib and placebo, they were counted as leniolisib patients only.
[a] Data from completed trials up to 23-Sep-2025.
Completed studies include: CCDZ173X2203 and CCDZ173X2201/E1.
Ongoing studies with interim CSR (exposure as in interim CSR) available: LE 3301 (n=21), LE 4301 (n=3).

Table SIII.4: Exposure per ethnic origin

	Ethnic origin	Number of subjects[a] (n)
Healthy volunteers and subjects (all indications)	Caucasian	206
	Black	57
	Asian	24
	Other	27
	Total	314
Subjects with APDS	Caucasian	41
	Black	2
	Asian	9
	Other	10
	Total	62

[a] Data from completed trials up to 23-Sep-2025.
Completed studies include: CCDZ173X2101, CCDZ173X2102, CCDZ173X2104, CCDZ173X2203, CCDZ173X2201/E1, LE 1101, LE 1102, LE 2101 and LE 5101.
Ongoing studies with interim CSR (exposure as in interim CSR) available: LE 3301 (n=21), LE 4301 (n=3).

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

The main exclusion criteria in the adult and adolescent APDS clinical development program are listed in Table SIV.1.

Table SIV.1: Main exclusion criteria in clinical trials with leniolisib

Exclusion criterion	Reason for exclusion criterion	Is it considered to be included as missing information?	Rationale
Liver disease or liver injury as indicated by clinically significant abnormal liver function tests. Alanine amino-transferase (ALT) and aspartate aminotransferase (AST) greater than 2.5 times upper limit of normal (ULN).	Severe comorbidity was excluded to avoid confounding of the pharmacokinetics (PK) and safety parameters.	Yes	Hepatic impairment may impact leniolisib exposure therefore safety in patients with hepatic impairment is included as missing information.
Use of an mTOR inhibitor (e.g., sirolimus (rapamycin), everolimus) or a PI3Kδ inhibitor (selective or non-selective PI3K inhibitors) within 6 weeks prior to first dosing, however short-term use for up to a total of 5 days was allowed but only up to 1 month prior to enrolment in the study.	To allow assessment of leniolisib without confounders. Phosphoinositide 3-kinases (PI3K) are lipid kinases and are pivotal signal transducers involved in physiological and pathologic cell functions. Their principal function is the generation of phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 serves as an important cellular second messenger activating Akt (via PDK1) and regulating a multitude of cellular processes such as proliferation, differentiation, cytokine production, cell survival, angiogenesis and metabolism. Both loss of function and gain of function PI3Kδ mutations lead to	No	These treatments are not approved for treatment of APDS and off-label use is within the discretion of the physician.
B cell depleters (e.g., rituximab) within 6 months prior to first dosing of study medication; if patients had received prior treatment with a B cell depleter, absolute B lymphocyte counts in the blood were required to regain normal values.			

Table SIV.1: Main exclusion criteria in clinical trials with leniolisib

Exclusion criterion	Reason for exclusion criterion	Is it considered to be included as missing information?	Rationale
Belimumab or cyclophosphamide within 6 months prior to first dosing of study medication.	immunodeficiency syndromes. The PI3Kδ pathway requires modulation for optimal immune function that could be adversely impacted in the presence of other immunosuppressive agents leading to profound immune suppression. The appropriate function of the PI3Kδ pathway by leniolisib requires dampening but not complete suppression of the pathway as measured by pAkt and PS6 activity.		
Cyclosporine A, mycophenolate, 6-mercaptopurine, azathioprine or methotrexate within 3 months prior to first dosing of study medication.			
Glucocorticoids above 25 mg prednisone or equivalent per day within 2 weeks prior to first dosing of study medication.			
Other immunosuppressive medication where effects were expected to persist at start of dosing of study medication			
Current use of medication known to be strong inhibitor or moderate or strong inducers of isoenzyme CYP3A, if treatment cannot be discontinued or switched to a different medication prior to starting study treatment.	Interaction potential In vitro studies showed that leniolisib is a substrate for both CYP3A and P-gp. In a clinical interaction study, leniolisib exposure was increased (~2-fold) following concurrent administration of a strong dual inhibitor of CYP3A/P-gp, whereas a strong P-gp inhibitor had no effect. These results confirm the important role of CYP3A but not P-gp in the in vivo disposition of leniolisib. The contribution of CYP3A to	No	If CYP3A substrates were required to be used in the clinical development, protocols allowed for a pause in leniolisib administration during use of the CYP3A agent. A Drug-Drug Interactions Study LE 5101 has been completed and related relevant data have been implemented in the summary of product characteristics (SmPC) and package leaflet (PL) to instruct HCPs and patients.

Table SIV.1: Main exclusion criteria in clinical trials with leniolisib

Exclusion criterion	Reason for exclusion criterion	Is it considered to be included as missing information?	Rationale
	total clearance was estimated to be ~60%.		
Current use of medications that were metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index (drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)).	Interaction potential In vitro, leniolisib showed time-dependent inhibition of CYP1A2 and weak inhibition potential on several hepatic and renal uptake and efflux transporters but not P-gp.	No	If CYP1A2 substrates with a narrow therapeutic index were required to be used in the clinical development, protocols allowed for a pause in leniolisib administration during use of the CYP1A2 agent. A Drug-Drug Interactions Study LE 5101 has been completed and related relevant data have been implemented in the SmPC and PL to instruct HCPs and patients.
Administration of live vaccines (this includes any attenuated live vaccines) starting from 6 weeks before study entry, during the study and up to 7 days after the last dose of leniolisib.	Risk of adverse events. Caution is needed when administering live vaccines to patients with immune deficiencies. The effect, if any, of leniolisib on the effectiveness of live or attenuated vaccines is unknown, but no negative effect is expected. Immunocompromised patient populations are at greater risk for vaccine preventable illnesses, but great caution must be exercised in the administration of live and/or attenuated live vaccines to these populations (Sobh, 2016). There is concern for decreased efficacy and possible adverse events with administration of live or live attenuated vaccines in the presence of immune system modulating therapies in patients with primary immune	No	Patients with APDS have an inadequate response to vaccinations due to the natural course of APDS in childhood and adolescence (Bloomfield, 2021) and impaired antibody response to vaccines as part of the clinical symptoms of APDS (Ewertowska, 2020). Leniolisib treatment aims to restore the immune deficiency caused by APDS by correcting of the dysregulated T cells and B cells. There is no indication that leniolisib would negatively affect the response to vaccines beyond what would be anticipated in the APDS disease state. In conclusion, the risk of administration of a live vaccine is a risk due to the underlying immunodeficiency and is not related to leniolisib but may be related to the immunodeficiency associated

Table SIV.1: Main exclusion criteria in clinical trials with leniolisib

Exclusion criterion	Reason for exclusion criterion	Is it considered to be included as missing information?	Rationale
	deficiencies.		with the disease state.
Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.	Leniolisib can cause foetal harm based on findings from animal studies.	No	It is unethical to plan studies with leniolisib during pregnancy and/or lactation. Relevant instructions are implemented in the SmPC and PL to inform appropriately HCPs and patients.
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing of study medication and for 2 days after stopping study treatment.			

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Due to the extremely low prevalence of APDS in the general population, the clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse events. In addition, the heterogeneous nature of APDS can make it difficult to differentiate adverse events due to therapy from the natural history of the disease due to the highly variable phenotypic expression of the underlying disease and the change in presentation of the disease over time. See Part II: Module SIII for clinical trial exposure data.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in the clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development program

Type of special population	Exposure
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with disease severity different from inclusion criteria in clinical trials	Immunocompromised patients with APDS were an inclusion criterion. Patients with renal, hepatic, or cardiovascular impairment were not included in the clinical trials. A formal hepatic impairment study (LE 6101) to assess the impact of moderate and severe hepatic impairment on the pharmacokinetics of leniolisib is ongoing.
Population with relevant different ethnic origin	Patients of all ethnic origins were eligible in the clinical development program. Although the majority were Caucasian, there were also Asian and Afro-American patients included.
Subpopulations carrying relevant genetic polymorphisms	APDS is categorized as one of two mutations, PIK3CD/P110δ (APDS1) or PIK3R1/P85α (APDS2). Both subpopulations were included in the clinical development program.
Other	The number of elderly patients in the leniolisib clinical development program overall is low. Three patients between 65-75 years were included in the primary Sjogren's Syndrome study (CCDZ173X2203). In the APDS clinical trials, there have been no patients 65 years or older due to the reduced life expectancy of these patients. There is no indication that leniolisib will be less effective in elderly patients.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

Leniolisib has been commercialised in the US after its marketing approval by the FDA on 24-Mar-2023. Since then, marketing authorization has been granted in Israel, the United Kingdom, and Australia.

Cumulative exposure since first approval was estimated to be 138 US patients at the DLP of PSUR # 05 (23-Sep-2025).

Exposure was calculated based on commercial product shipment data. All patients received Joenja 70 mg film-coated tablets BID.

Cumulatively, 2702 bottles of Joenja were shipped worldwide (2419 US and 283 EU/rest of world [ROW]) corresponding to a patient-year exposure of 225. The number of unique US patients cumulatively having been provided at least 1 dose of Joenja is 138. The number of unique EU/ROW patients cumulatively was not available at the DLP of PSUR #05.

Detailed data on sex and age are not available.

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

Potential for misuse for illegal purposes

The product has no properties which would attract misuse for illegal purposes.

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:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

In general, treatment with leniolisib was well-tolerated and most adverse events observed during the clinical development program were assessed as disease-related and not related to treatment with leniolisib. Table SVII.1 presents the events included in the proposed Section 4.8 of the SmPC.

Table SVII.1: Adverse reactions

System organ class	Adverse reaction	Frequency	Comment
Nervous system disorders	Headache	Very common	Low impact, spontaneous recovery during continued treatment. Corrective treatment with over-the-counter paracetamol is usually effective.
Gastrointestinal disorders	Vomiting	Very common	Low impact, spontaneous recovery during continued treatment. According to investigator often related to APDS-enteropathy.
	Dyspepsia	Common	
Skin and subcutaneous tissue disorders	Alopecia	Very Common	Low impact, spontaneous recovery during continued treatment. According to investigator often related to APDS-related non-infectious skin disease.
	Atopic dermatitis*	Common	
	Rash	Common	Low impact. Corrective treatment with standard of care with/without temporarily stopping Joenja
General disorders and administration site conditions	Fatigue	Common	Low impact, spontaneous recovery during continued treatment. According to investigator often related to APDS-related infections and other conditions.
Investigations	Weight increased	Very common	Impact for individual patient dependent on fact if weight increase is desired or not.
	Neutrophil count decreased	Very common	Low impact, spontaneous recovery during continued treatment. Nadir at D15. Asymptomatic.

*Dermatitis atopic: including dermatitis atopic and eczema

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

SVII.1.2.1 Important identified risks

No important identified risks have been associated with leniolisib treatment to date.

SVII.1.2.2 Important potential risks

The important potential risks of

- Serious diarrhoea/colitis

- Serious hepatotoxicity
- Serious and opportunistic infections
- Pneumonitis
- Severe cutaneous adverse events (SCAR)

are considered class-effects of PI3K inhibitors approved for treatment of haematological and solid cancers.

These adverse events (AEs) are related to stimulation of the immune system and have been reported for PI3K inhibitors, BTK inhibitors, anti-apoptotic protein BCL-2 inhibitors, JAK inhibitors, CAR-T cell therapy and immune checkpoint inhibitors. They can affect many organs, including lungs, pancreas, liver, skin, heart etc. Frequency is common to very common in these drugs indicated for the treatment of haematological and solid cancers.

No such events have been associated with leniolisib treatment in the APDS clinical development program. They are nevertheless considered important potential risks for leniolisib because of the association with the class and the characterization of the individual risks is presented in Table SVII.2 to Table SVII.6.

Risk-benefit impact:

These AEs with other PI3K inhibitors used in oncology were frequent (occurring in >10% of patients) and have been serious, with sometimes fatal outcome.

Important potential risk: Embryo-foetal toxicity

Embryo-foetal toxicity is seen in pre-clinical studies showing microphthalmia after maternal exposure at high doses in rats (C_{max} 4.7 x human exposure, AUC 6.6 x) and rabbits (C_{max} 7.2 x human exposure, AUC 2.3 x). In the clinical development programme, pregnancy, and the wish to become pregnant, were exclusion criteria. In the younger paediatric development program, juvenile toxicity data supports study drug exposure in patients one year of age or older. Embryo-foetal toxicity is an important potential risk for leniolisib since no human data are available and the risk is considered a class effect of PI3K inhibitors. Characterisation of the risk is presented in Table SVII.7.

Risk-benefit impact:

Patients using leniolisib are advised not to get pregnant, as there is insufficient information available to assess the risk in human. Since pregnancy is theoretically avoidable and should be considered in advance in patients with APDS due to the autosomal dominant inheritance pattern, this will not affect the benefit-risk balance of the product.

SVII.1.2.3 Missing information

Missing information: Safety in patients with hepatic impairment

Patients with APDS with ALT and AST greater than 2.5 times upper limit of normal (ULN) were excluded from the study CCDZ173X2201 Part 1, Part 2 and E1.

No formal hepatic impairment studies have been conducted with leniolisib. Pharming has initiated a formal hepatic impairment study (LE 6101) to assess the impact of moderate and severe hepatic impairment on the pharmacokinetics of leniolisib. A protocol is available in Annex 3. The final report of this study is expected to be available by June 2026. Pharming commits to submit the study report to EMA and amend the RMP and product information as needed in a timely fashion.

Risk-benefit impact:

Hepatic impairment may impact leniolisib exposure: leniolisib was 60% metabolized by the liver, with CYP3A4 as the most predominant enzyme (95.4%) involved in the primary oxidative metabolism of leniolisib, with minor contribution from other enzymes (3.5% CYP3A5, 0.7% CYP1A2 and 0.4% CYP2D6). The strong activity of recombinant CYP1A1 suggests a possible involvement of this enzyme in the biotransformation of leniolisib in extrahepatic tissues. It is therefore not excluded that exposure is increased in patients with hepatic impairment. The hepatic impairment study (LE 6101) will provide the required information.

Missing information: Long-term safety

Pharming conducted an open-label non-randomized study (study CCDZ173X2201E1) to evaluate long-term safety, tolerability, efficacy, and PK of leniolisib. The study was terminated for non-safety related reasons in Jan 2025; the final study report has been submitted.

In addition, a Post-authorization Effectiveness and Safety Study (SOB1, LE 4401) is planned. Details are provided in Part III.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is the 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

Table SVII.2: Important potential risk: Serious diarrhoea/Colitis

Name of the risk	Serious diarrhoea/colitis
MedDRA search strategy	Non-infectious diarrhoea (Standardized MedDRA Query [SMQ)] (Broad) High level term (HLT) Colitis (excl infective)
Potential mechanism	Class-effect of PI3K inhibitors (-lisibs). Off-target pharmaco-dynamic effect. With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell survival and function. It is thought that the decreased T regulatory cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products (FDA Briefing document PI3K inhibitors in hematologic malignancies, 2022). The effect is potentially less with leniolisib at a dose of 70 mg BID for APDS, as the PI3Kδ inhibition is not complete, but in the order of about 78%. Leniolisib in APDS aims at restoring normal immune function, not at complete inhibition of the pathway for a maximal cytotoxic effect as in other PI3K inhibitors used in haematologic or solid cancer.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	No AEs, such as serious diarrhoea/colitis, have been reported in healthy volunteers or patients with APDS treated with leniolisib with single doses of 10-400 mg or repeated doses up to 140 mg BID for 15 days. Non-clinical studies with leniolisib resulted in reduced immune function, resulting in opportunistic infections in the GI-tract and skin, leading to mortality and moribundity at the highest doses (300 mg/kg/day in rats) in the repeated dose toxicity studies (Non-clinical overview, Module 2.4). AEs like diarrhoea/colitis (≥ grade 3), etc. are considered a class-effect of PI3K inhibitors approved for treatment of haematological and solid cancers with a frequency of "very common" (idelalisib monotherapy 12-43% all grades and 0-16% ≥ grade 3; duvelisib monotherapy 31-77.8% all grades and 9.1-25.8% ≥ grade 3 [Pilmis, 2023; Hanlon & Brander, 2020]).
Characterization of the risk (frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, impact on quality of life)	Frequency *Clinical* The serious diarrhoea/colitis rate for leniolisib in the double-blind study (duration 12 weeks) was 0% in both leniolisib arm and the placebo arm. To date, 3 cases pertaining to the risk of serious diarrhoea/colitis reporting Colitis (2) and Gastroenteritis (1) were received from the clinical development program which were assessed as not related to leniolisib by the investigator and MAH. Diarrhoea and colitis are also APDS-related signs and symptoms, which often improved during leniolisib treatment.\

Table SVII.2: Important potential risk: Serious diarrhoea/Colitis

Name of the risk	Serious diarrhoea/colitis
	Post-marketing To date, 10 cases pertaining to the risk of serious diarrhoea/colitis reporting Colitis (6), Diarrhoea (2) Enteritis (1) and Gastroenteritis (1) were received from expanded access programs (EAP) and/or post-marketing use. All events were assessed as not related to leniolisib by the MAH. Absolute risk In study CCDZX2201 extension: 1/37 patients = 2.7 % colitis, no ≥ grade 3 diarrhoea. Relative risk There is no information on the risk compared to placebo, as no events of severe diarrhoea or colitis were observed on leniolisib or placebo in study CCDZX2201 part 2. Severity One clinical case of Colitis on leniolisib was grade 3, for the other case severity was not reported. No grade 4 or grade 5 cases of severe diarrhoea or colitis have been reported in the clinical program. The cases from EAP and post-marketing sources were of grade 3 (1), moderate (5) or mild (1) severity (if reported). Causality No leniolisib-related cases of diarrhoea/colitis have been reported to date. Long-term outcome All cases were either resolved or the outcome was not reported/unknown, except two non-related cases of Colitis from post-marketing use that were reported as not resolved. Impact on quality of life Serious diarrhoea or colitis have a negative impact on quality of life. Interviews with patients have shown that the reduction of the diarrhoea due to leniolisib has a positive impact on the quality of life (QoL). Several patients reported that their diarrhoea disappeared since they started leniolisib.
Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors)	It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to AEs such as severe diarrhoea/colitis than the partial inhibition needed for restoring normal immune function in patients with APDS. In idelalisib patients, serious diarrhoea/colitis, even with intestinal perforation, was a late event, with 20% diarrhoea/colitis of any grade at 2 months (< 5% ≥ grade 3) and > 50% at 32 months (> 35% ≥ grade 3) (Hanlon & Brander, 2020; Coutré, 2015).
Preventability	There is no information on the preventability of diarrhoea or colitis.
Impact on the benefit-risk balance of the product	To date, no leniolisib-related serious diarrhoea/colitis have been observed. The opposite is rather the case. The reduction in APDS-related diarrhoea over time had a positive impact on the patient's QoL and on the benefit/risk balance of the product.
Public health impact	Public health impact is low, as APDS is an orphan disease with an estimated frequency of 1:1,000,000 persons. Therefore, the number of patients potentially affected by AEs such as severe diarrhoea/colitis is very low.

Table SVII.2: Important potential risk: Serious diarrhoea/Colitis

Name of the risk	Serious diarrhoea/colitis
Text proposal for Section 4.4	Class-label warning to inform prescribers that serious side effects have been reported for other PI3K inhibitors for oncology indications: Immune-related adverse events Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other PI3K delta inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in patients with APDS. Joenja is not approved for treatment of haematological or solid cancers.
Text proposal for Section 4.8	Not applicable, as related diarrhoea or colitis have not yet been reported during treatment with leniolisib.

Table SVII.3: Important potential risk: Serious hepatotoxicity

Name of the risk	Serious hepatotoxicity
MedDRA search strategy	Hepatic disorders (SMQ) (Broad)
Potential mechanism	Class-effect of PI3K inhibitors (-lisibs). Off-target pharmacodynamic effect. With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell survival and function. It is thought that the decreased T regulatory cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products (FDA Briefing document PI3K inhibitors in hematologic malignancies, 2022). The effect is potentially less with leniolisib at a dose of 70 mg BID for APDS, as the PI3Kδ inhibition is not complete, but in the order of about 78%. Leniolisib in APDS aims at restoring normal immune function, not at complete inhibition of the pathway for a maximal cytotoxic effect as in other PI3K inhibitors used in haematologic or solid cancer.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	No AEs, such as serious hepatotoxicity, have been reported in healthy volunteers or patients with APDS treated with leniolisib with single doses of 10-400 mg or repeated doses up to 140 mg BID for 15 days. No effect on liver was reported from non-clinical studies (Non-clinical overview, Module 2.4). AEs like serious hepatotoxicity and ALT/AST increase ≥ grade 3 are considered a class-effect of PI3K inhibitors approved for treatment of haematological and solid cancers with a frequency of "very common" (idelalisib: 14-23%, Cuneo, 2019; Hanlon & Brander, 2020) or "common" (duvelisib: 10.9-40%%, Hanlon & Brander, 2020; Flinn, 2019).
Characterization of the risk (frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, impact on quality of life)	Frequency *Clinical* The frequency of ALT/AST increase ≥ grade 3 in the double-blind study (duration 12 weeks) was 0% in both the leniolisib arm and the placebo arm. To date, 2 cases pertaining to the risk of serious hepatotoxicity reporting Alanine aminotransferase increased (1) and Hepatitis acute (1) were received from the clinical development program and assessed as unlikely/not related to leniolisib by the investigator and MAH. *Post-marketing* To date, 3 cases pertaining to the risk of serious hepatotoxicity reporting Hepatic cirrhosis (2) and Portal hypertension (1) were received from EAP and/or post-marketing use. The events were assessed as not related to leniolisib by the MAH.

Table SVII.3: Important potential risk: Serious hepatotoxicity

Name of the risk	Serious hepatotoxicity
	Absolute risk In study CCDZX2201 part 1: 0/6 patients = 0% ALT/AST increase ≥ grade 3 In study CCDZX2201 part 2: 0/21 patients = 0% ALT/AST increase ≥ grade 3 Relative risk There is no information on the risk compared to placebo, as no events of ALT/AST increase ≥ grade 3 were observed on leniolisib or placebo in study CCDZX2201 part 2. Severity For one clinical case of ALT increase that occurred on leniolisib no severity was reported. For the other clinical case of Hepatic acute, the severity was reported as grade 3. For the other events reported in post-marketing use, no severity was reported. Causality All cases were assessed by the MAH as unlikely/not related to leniolisib. Long-term outcome The two clinical cases were reported as resolved. For the other events the outcome was not reported/unknown. Impact on quality of life ALT/AST increases of grade 3 are generally asymptomatic.
Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors)	It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these AEs than the partial inhibition needed for restoring normal immune function in patients with APDS. In idelalisib patients, increased ALT/AST was an early event, occurring predominantly within the first 12 weeks of treatment. Serious hepatotoxicity was reported in 12% of patients (Coutré, 2015) and in 2-23% (Hanlon & Brander, 2020).
Preventability	There is no information on the preventability of ALT/AST increases ≥ grade 3. Monitoring can identify increases of ALT/AST at an earlier grade.
Impact on the benefit-risk balance of the product	As transient and unrelated increases in ALT/AST grade 3 during leniolisib treatment were asymptomatic, there was no impact on the benefit/risk balance of the product.
Public health impact	Public health impact is low, as APDS is an orphan disease with an estimated frequency of 1:1,000,000 persons. Therefore, the number of patients potentially affected by these AEs is very low.
Text proposal for Section 4.4	Class-label warning to inform prescribers that serious side effects have been reported for other PI3K inhibitors: Immune-related adverse events Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other PI3K delta inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in patients with APDS. Joenja is not approved for treatment of haematological or solid cancers.
Text proposal for Section 4.8	Not applicable, as serious hepatotoxicity or related ALT/AST increases ≥ grade 3 have not been reported with leniolisib.

Table SVII.4: Important potential risk: Serious and opportunistic infections

Name of the risk	Serious and opportunistic infections
MedDRA search strategy	Opportunistic infections (SMQ) (Broad)
Potential mechanism	Class-effect of PI3K inhibitors (-lisibs). Off-target pharmaco-dynamic effect. With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell survival and function. It is thought that the decreased T regulatory cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products (FDA Briefing document PI3K inhibitors in hematologic malignancies, 2022). Infections, especially serious and opportunistic infections are due to the immune-depressive effect of complete PI3K blockade. Rohrbacher concluded that idelalisib interfered with the functions of T and NK cells from both healthy donors and CLL patients. The in vitro data suggest that idelalisib-induced impairment of T and NK-cell function contributes to an increased rate of infections regardless of the underlying B-cell malignancy (Rohrbacher, 2021). The effect is potentially less with leniolisib at a dose of 70 mg BID for APDS, as the PI3Kδ inhibition is not complete, but in the order of about 78%. Leniolisib in APDS aims at restoring normal immune function, not at complete inhibition of the pathway for a maximal cytotoxic effect as in other PI3K inhibitors used in haematologic or solid cancer.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	No AEs such as serious or opportunistic infections have been reported in healthy volunteers or patients with APDS treated with leniolisib with single doses of 10-400 mg or repeated doses up to 140 mg BID for 15 days. Non-clinical studies with leniolisib resulted in reduced immune function, resulting in opportunistic infections in the GI-tract and skin, leading to mortality and moribundity at the highest doses (300 mg/kg/day in rats) in the repeated dose toxicity studies (Non-clinical overview, Module 2.4). AEs like serious infection (≥ grade 3), etc. are considered a class-effect of PI3K inhibitors approved for treatment of haematological and solid cancers with a frequency of "very common" (idelalisib 7-20%; duvelisib 10->23.6% [Pilmis, 2023; Hanlon & Brander, 2020]). Serious and fatal infections have occurred with idelalisib, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (Rohrbacher, 2021). Prophylaxis for PJP should therefore be administered to all patients throughout idelalisib treatment, and for a period of 2 to 6 months after discontinuation [SmPC ZYDELIG].
Characterization of the risk (frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, impact on quality of life)	<u>Frequency</u> *Clinical* The serious infection rate for leniolisib in the double-blind study (duration 12 weeks) was 0% in the leniolisib arm and 10% in the placebo arm. To date, 5 cases pertaining to the risk of serious and opportunistic infections reporting COVID-19 (2), Metapneumovirus infection (1), Parainfluenzae virus infection (1) and Staphylococcal bacteraemia (1) were received from the clinical development program. All events were assessed as not related to leniolisib by the investigator and MAH. Patients with APDS have a high baseline infection rate associated with their underlying immune deficiency. In fact, the frequency of infections in patients with APDS treated with leniolisib gradually decreased over time and continued to decrease over the years. Infections are the hallmark of APDS and leniolisib restores the immune deficiency caused by APDS, which resulted in a decrease in the frequency of infections, a decrease in the need for Ig replacement therapy without increase in the need for antibiotic treatment.

Table SVII.4: Important potential risk: Serious and opportunistic infections

Name of the risk	Serious and opportunistic infections
	Post-marketing To date, 24 cases pertaining to serious and opportunistic infections were received from EAP and/or post-marketing use reporting Influenza (3), Sepsis (3), Septic shock (3), COVID-19 (2), Pneumonia staphylococcal (2), Pseudomonas infection (2), and Atypical pneumonia, Clostridium difficile colitis, Cytomegalovirus colitis, Epstein-Barr virus infection re-activation, Meningitis pneumococcal, Metapneumovirus infection, Neutropenic sepsis, Pneumococcal bacteraemia, Pneumonia klebsiella, Pneumonia pneumococcal, Pneumonia pseudomonal, Septic arthritis streptococcal, Staphylococcal infection, Staphylococcal sepsis and Visceral leishmaniasis reported once. All events were assessed as not related to leniolisib by the MAH. Absolute risk In study CCDZX2201 part 1: 0/6 patients = 0% serious infections In study CCDZX2201 part 2: 0/21 patients = 0% serious infections Of these infections, none had a preferred term (PT) included in the MedDRA SMQ opportunistic infections narrow. Relative risk In study CCDZX2201 part 2: 0/21 patients = 0% serious infections on leniolisib versus 1/10 patients = 10% on placebo. Severity Four of the clinical events were grade 3/severe, and 1 was mild. Of the 30 EAP/post-marketing events, 7 had severity reported: mild (2), moderate (1), severe (4). Causality All serious infections were assessed as not related to leniolisib. Long-term outcome Of the clinical cases, all were reported as recovered. Of the 30 events reported in the 24 EAP/post-marketing cases, 12 events were resolved/resolving, 8 events had outcome not reported/unknown, 4 were not recovered and 6 events were fatal: Septic shock (3). Metapneumovirus infection (1), Pneumonia klebsiella (1) and Pneumonia staphylococcal (1). Impact on quality of life Infections have a negative impact on quality of life. Interviews with patients have shown that the reduction of the infection rate due to leniolisib has a positive impact on the QoL. Several patients reported that there were no hospitalizations for infection anymore since they started leniolisib.
Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors)	Pre-existing lung diseases, like chronic obstructive pulmonary disease (COPD), bronchiectasis and asthma and smoking have been associated with an increased risk of opportunistic infections such as PJP and bacterial pneumonia (Cuneo, 2019). It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these AEs than the partial inhibition needed for restoring normal immune function in patients with APDS.
Preventability	Infections can be prevented by barrier measures and vaccination. PJP prophylaxis is administered routinely to patients on other PI3Kδ inhibitors (SmPC ZYDELIG) in oncology indications but is not required in patients with APDS treated with leniolisib.
Impact on the benefit-risk balance of the product	To date, no leniolisib-related serious or opportunistic infections have been observed. The opposite is rather the case. The reduction in infection rate over time has a positive impact on the patient's QoL and on the benefit/risk balance of the product.

Table SVII.4: Important potential risk: Serious and opportunistic infections

Name of the risk	Serious and opportunistic infections
Public health impact	Public health impact is low, as APDS is an orphan disease with an estimated frequency of 1:1,000,000 persons. Therefore, the number of patients potentially affected by AEs such as opportunistic infections is very low.
Text proposal for Section 4.4	Class-label warning to inform prescribers that serious side effects have been reported for other PI3K inhibitors: Immune-related adverse events Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other PI3K delta inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in APDS patients. Joenja is not approved for treatment of haematological or solid cancers.
Text proposal for Section 4.8	Not applicable, as related serious or opportunistic infections have not been reported during treatment with leniolisib.

Table SVII.5: Important potential risk: Pneumonitis

Name of the risk	Pneumonitis
MedDRA search strategy	For pneumonitis: system organ class (SOC) Respiratory disorders with manual check (still feasible with low numbers of patients with the disease and low number of AEs per patient)
Potential mechanism	Class-effect of PI3K inhibitors (-lisibs). Off-target pharmacodynamic effect. With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell survival and function. It is thought that the decreased T regulatory cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products (FDA Briefing document PI3K inhibitors in hematologic malignancies, 2022). The effect is potentially less with leniolisib at a dose of 70 mg BID for APDS, as the PI3Kδ inhibition is not complete, but in the order of about 78%. Leniolisib in APDS aims at restoring normal immune function, not at complete inhibition of the pathway for a maximal cytotoxic effect as in other PI3K inhibitors used in haematologic or solid cancer.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	No AEs, such as pneumonitis, have been reported in healthy volunteers or patients with APDS treated with leniolisib with single doses of 10-400 mg or repeated doses up to 140 mg BID for 15 days. Non-clinical studies with leniolisib resulted in reduced immune function, resulting in opportunistic infections in the GI-tract and skin, leading to mortality and moribundity at the highest doses (300 mg/kg/day in rats) in the repeated dose toxicity studies (Non-clinical overview, Module 2.4). AEs like pneumonitis are considered a class-effect of PI3K inhibitors approved for treatment of haematological and solid cancers, with a frequency of "common": 3-13% (all grades) resp. 1.4-6.4% (≥ grade 3, including cases with fatal outcome) for idelalisib (Hus, 2022; Hanlon & Brander, 2020) and a frequency of "common": 4-11% for duvelisib (Hanlon & Brander, 2020).
Characterization of the risk (frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, impact on quality of life)	Frequency *Clinical* The pneumonitis rate for leniolisib in the double-blind study (duration 12 weeks) was 0% in both the leniolisib and the placebo arm. To date, no cases pertaining to the risk of pneumonitis were reported from the clinical development program.

Table SVII.5: Important potential risk: Pneumonitis

Name of the risk	Pneumonitis
	Post-marketing To date, no cases pertaining to the risk of pneumonitis have been received from post-marketing reporting. Absolute risk In study CCDZX2201 part 1: 0/6 patients = 0% pneumonitis In study CCDZX2201 part 2: 0/21 patients = 0% pneumonitis Relative risk There is no information on the risk compared to placebo, as no events of pneumonitis were observed on leniolisib or placebo in study CCDZX2201 part 2. Severity Not applicable. Causality Not applicable. Long-term outcome Not applicable. Impact on quality of life Not applicable.
Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors)	To date, no pneumonitis has been observed during leniolisib treatment. Risk factors have therefore not been identified.
Preventability	Monitoring for AEs
Impact on the benefit-risk balance of the product	To date, no cases of pneumonitis have been reported in leniolisib-treated patients. An impact on the benefit-risk balance is therefore not applicable.
Public health impact	Public health impact is low, as APDS is an orphan disease with an estimated frequency of 1:1,000,000 persons. Therefore, the number of patients potentially affected by these AEs is very low.
Text proposal for Section 4.4	Class-label warning to inform prescribers that serious side effects have been reported for other PI3K inhibitors: Immune-related adverse events Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other PI3K delta inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in patients with APDS. Joenja is not approved for treatment of haematological or solid cancers.
Text proposal for Section 4.8	Not applicable, as pneumonitis has not been reported during treatment with leniolisib.

Table SVII.6: Important potential risk: SCAR

Name of the risk	Severe cutaneous adverse reactions (SCAR)
MedDRA search strategy	Severe cutaneous adverse reactions (SMQ) (Broad) Drug reaction with eosinophilia and systemic symptoms (SMQ) (Broad)

Table SVII.6: Important potential risk: SCAR

Name of the risk	Severe cutaneous adverse reactions (SCAR)
Potential mechanism	Class-effect of PI3K inhibitors (-lisibs). Off-target pharmaco-dynamic effect. With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell survival and function. It is thought that the decreased T regulatory cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products (FDA Briefing document PI3K inhibitors in hematologic malignancies, 2022). The effect is potentially less with leniolisib at a dose of 70 mg BID for APDS, as the PI3Kδ inhibition is not complete, but in the order of about 78%. Leniolisib in APDS aims at restoring normal immune function, not at complete inhibition of the pathway for a maximal cytotoxic effect as in other PI3K inhibitors used in haematologic or solid cancer.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	No AEs, such as SCAR, have been reported in healthy volunteers or patients with APDS treated with leniolisib with single doses of 10-400 mg or repeated doses up to 140 mg BID for 15 days. Non-clinical studies with leniolisib resulted in reduced immune function, resulting in opportunistic infections in the GI-tract and skin, leading to mortality and moribundity at the highest doses (300 mg/kg/day in rats) in the repeated dose toxicity studies (Non-clinical overview, Module 2.4). AEs like severe cutaneous adverse events are considered a class-effect of PI3K inhibitors approved for treatment of haematological and solid cancers with a frequency of "common" (all grade 10-58%, ≥ grade 3 2-13%, Hus, 2022). One case of toxic epidermal necrolysis (TEN) occurred in a study of idelalisib in combination with rituximab and bendamustine. Gabriel reported a case of exfoliative dermatitis affecting > 90% of the patient's body surface on idelalisib monotherapy (Gabriel, 2017). Other severe or life-threatening (Grade ≥3) cutaneous reactions, including dermatitis exfoliative, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash, and skin disorder, have been reported in idelalisib-treated patients. Monitor patients for the development of severe cutaneous reactions and discontinue idelalisib (SmPC ZYDELIG). For duvelisib, SCAR all grade were reported in 16.2-42%, and ≥grade 3 in 5.2-15% (Hanlon & Brander, 2020).
Characterization of the risk (frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, impact on quality of life)	Frequency *Clinical* The frequency of SCAR ≥ grade 3 in the double-blind study (duration 12 weeks) was 0% in both leniolisib arm and the placebo arm. To date, no cases pertaining to the risk of SCAR were reported from the clinical development program. *Post-marketing* To date, no cases pertaining to the risk of SCAR have been received from EAP/post-marketing reporting. Absolute risk In study CCDZX2201 part 1: 0/6 patients = 0% SCAR In study CCDZX2201 part 2: 0/21 patients = 0% SCAR Relative risk There is no information on the risk compared to placebo, as no events of SCAR were observed on leniolisib or placebo in study CCDZX2201 part 2. Severity Not applicable. Causality Not applicable.

Table SVII.6: Important potential risk: SCAR

Name of the risk	Severe cutaneous adverse reactions (SCAR)
	Long-term outcome Not applicable. Impact on quality of life Not applicable.
Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors)	To date, no cases of SCAR have been observed during leniolisib treatment. Risk factors have therefore not been identified.
Preventability	Monitoring for AEs
Impact on the benefit-risk balance of the product	To date, no cases of SCAR have been reported in leniolisib-treated patients. An impact on the benefit-risk balance is therefore not applicable.
Public health impact	Public health impact is low, as APDS is an orphan disease with an estimated frequency of 1:1,000,000 persons. Therefore, the number of patients potentially affected by these AEs is very low.
Text proposal for Section 4.4	Class-label warning to inform prescribers that serious side effects have been reported for other PI3K inhibitors: Immune-related adverse events Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other PI3K delta inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in patients with APDS. Joenja is not approved for treatment of haematological or solid cancers.
Text proposal for Section 4.8	Not applicable, as SCARs have not been reported during treatment with leniolisib.

Table SVII.7: Important potential risk: embryo-foetal toxicity

Name of the risk	Embryo-foetal toxicity
MedDRA search strategy	Congenital, familial and genetic disorders (SMQ) Foetal disorders (SMQ) Neonatal disorders (SMQ) Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ) Termination of pregnancy and risk of abortion (SMQ)
Potential mechanism	Class-effect of PI3K inhibitors (-lisibs). A warning is included in the SmPC or USPI of all approved PI3K inhibitors. Given the fact that the embryofoetal toxicity was seen in rats and rabbits treated with high doses of leniolisib, it cannot be excluded that complete blockade of the PI3K pathway may be responsible for the embryofoetal toxicity. In contrast to PI3K inhibitors used to treat haematological and solid cancers, leniolisib does not completely block the PI3K pathway.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	Embryo-foetal development studies in rats and rabbits have been performed. In rats at doses of 120 mg/kg/day, microphthalmia/ anophthalmia was evident and considered to be related to leniolisib. In rabbit studies (dose-range finding study and main study) there was no biologically relevant increase in the incidence of embryo-foetal variations and malformations or any sign for a teratogenic effect of leniolisib up to 30 mg/kg/day. At higher doses (100 mg/kg/day) maternal toxicity (body weight loss) was evident and in one litter two foetuses showed

Table SVII.7: Important potential risk: embryo-foetal toxicity

Name of the risk	Embryo-foetal toxicity
	microphthalmia. Considering the microphthalmia in rats, a test item relationship in rabbits cannot be excluded. Based on these data, it can be concluded that leniolisib is teratogenic in rats at doses of 120 mg/kg/day. The NOAEL for maternal toxicity and the no observed effect level (NOEL) for embryo-foetal development in rats were established at 30 mg/kg/day.
Characterization of the risk (frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, impact on quality of life)	Frequency *Clinical* There is no information available on the risk in humans, as no pregnancies have been reported from the clinical development program. *Post-marketing* To date, no cases pertaining to the risk of Embryo-foetal toxicity have been received from EAP/post-marketing reporting. Impact on quality of life Impact on quality of life will depend on the nature of embryo-foetal toxicity, if it occurs, but can be high.
Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors)	Women of child-bearing potential.
Preventability	Risk communication to prescribers, pharmacies and patients. Avoidance of pregnancy is possible using adequate contraception.
Impact on the benefit-risk balance of the product	The risk-benefit balance remains positive, as APDS is a very serious condition for which no other disease-modifying targeted treatment is available. Moreover, APDS is a genetic disease with an autosomal dominant inheritance pattern, so that patients will generally avoid pregnancy unless pre-implantation testing can be performed.
Public health impact	Public health impact is low, as APDS is an orphan disease with an estimated frequency of 1:1,000,000 persons. Therefore, the number of female patients potentially getting pregnant during treatment with leniolisib is very low.
Text proposal for Section 4.4	Women of childbearing potential Women of childbearing potential should use highly effective contraception while taking Joenja and for 1 week after the last dose (see Section 4.6).
Text proposal for Section 4.6	Women of childbearing potential/contraception in females Women of childbearing potential should use highly effective methods of contraception during treatment with Joenja and for 1 week after the last dose. Leniolisib can cause fetal harm based on findings from animal studies. Verify pregnancy status in females of reproductive potential prior to initiating treatment with Joenja. Pregnancy There are no data from the use of leniolisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Joenja is not recommended during pregnancy and in women of childbearing potential not using highly effective methods of contraception.

SVII.3.2 Presentation of the missing information

Missing Information: Safety in patients with hepatic impairment

Evidence source:

Clinical

Patients with alanine transaminase and aspartate transaminase greater than 2.5 times upper limit normal were excluded from Study CCDZ173X2201 Parts 1 and 2.

The risk of increased exposure cannot be excluded in patients with hepatic impairment as leniolisib was 60% metabolized by the liver, with CYP3A4 as the most predominant enzyme involved (95.4%) in the primary oxidative metabolism of leniolisib, with minor contribution from other enzymes (3.5% CYP3A5, 0.7% CYP1A2 and 0.4% CYP2D6).

To date, no serious adverse events have been reported from the clinical development program in patients with hepatic impairment.

A clinical study in patients with moderate and severe hepatic impairment is ongoing (LE 6101). No significant safety findings were received to date.

Post-marketing

To date, 5 cases have been reported from EAP/post-marketing use in patients with suspected hepatic impairment. The MAH assessed the events in 4 cases as not related.

- A fatal case report regarding a patient with underlying chronic Graft-versus-host-disease of the liver and Hodgkin Lymphoma stage IV reporting Pneumonia klebsiella and Septic shock.
- A patient with underlying Hepatic cirrhosis who experienced Septic arthritis streptococcal.
- A patient with underlying Hepatitis C, Hepatic cirrhosis and Portal hypertension reporting Fall and a Foot fracture.
- A patient with underlying Hepatic cirrhosis and Hepatitis C who presented with Splenomegaly, Pyrexia, Nausea, Bacterial translocation, Rectal haemorrhage, Haematochezia, Abdominal pain, and Iron deficiency.

The 5th case concerned a patient with a liver transplant in 2014 who experienced Arthralgia, Cytomegalovirus colitis, Clostridium difficile colitis, and Rash. The MAH assessed the non-serious events of Arthralgia and Rash as related, and the serious events of Cytomegalovirus colitis and Clostridium difficile colitis as not related to leniolisib.

Population in need of further characterisation:

As a result, SmPC Section 4.2 “Posology and method of administration” states that leniolisib has not been studied in patients with hepatic impairment and use of Joenja in patients with moderate to severe hepatic impairment is not recommended.

Clinical study LE 6101 in patients with hepatic impairment is ongoing.

Anticipated risk/consequence of the missing information:

The anticipated risk is considered low, given the statement that leniolisib has not been studied in patients with hepatic impairment is included in SmPC Section 4.2, as well as use of Joenja in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C) is not recommended.

Missing Information: Long-term safety

Evidence source:

To evaluate the long-term safety, the patient exposure needs to be followed for a longer period of time to obtain sufficient information. In total, 37 patients have been followed in the open-label extension (OLE) study

(CCDZ173X2201E1), where the maximum exposure is approximately 7 years. Although the dataset is limited, long-term use appears consistent with the existing safety profile, with no new or unexpected safety concern identified.

The long-term safety data with leniolisib included 37 participants with APDS treated for at least one year, 31 participants (83.8%) for at least 2 years, and 10 participants (27.0%) had at least 5 years of leniolisib exposure. As most subjects either completed the 6 years or transitioned to commercial product the study was terminated early. The last subject last visit took place on 30-Jan-2025 and all remaining patients were transferred to EAP. The final clinical study report was finalised on 09-Sep-2025.

Overall, 91.9% of participants in the extension study experienced in total 511 treatment-emergent AEs. The most common AEs by SOC were infections and infestations (83.8%) and gastrointestinal disorders (67.6%). Of note, the most common AE by PT was SARS-CoV-2 test negative (40.5% of participants). COVID-19 was the second commonly reported AE in 12/37 participants (32.4%). Additional AEs reported in over 20% of participants were upper respiratory tract infection (27.0%), pyrexia (24.3%), and headache (21.6%). Study drug-related AEs (7) were experienced by 5 participants (13.5%).

The most common study drug-related AE was weight increased in 3 participants (8.1%). Other drug-related AEs were arthralgia, hyperglycaemia, and neutrophil count decreased. None of the study drug-related AEs led to discontinuation of study treatment or study withdrawal.

SAEs were experienced by 10 (27.0%) participants. The most common SOC for SAEs was infections and infestations (13.5%). The most common SAEs by PT were abdominal pain and pneumonia, both in 2 participants (5.4%). No other SAE was experienced by more than 1 participant. None of the SAEs were considered by the investigator to be related to the study drug. Four participants had the study drug temporarily interrupted due to SAEs, and for 1 participant, study drug was later permanently discontinued (Hodgkin's disease).

The rate of infections per year decreased with long-term exposure to leniolisib compared to the annualized rates of infection per year from the 12-week treatment period of study Part 2.

Hematology except neutrophil count decreased (Grade 1-3 neutropenia were observed in some patients), clinical chemistry, and urinalysis values were not notably affected, and there were no participants suspected to have drug-induced liver injury.

Overall, no clinical meaningful changes from baseline in the mean values of vital sign and ECG parameters were reported through the extension study.

Three cases were received from EAP/post-marketing use, reporting Dermatitis exfoliative, Gastroenteritis, Product dose omission issue and Weight increased after use of leniolisib >2 years. All events were reported once, and all were assessed by the MAH as not related to leniolisib.

Population in need of further characterisation:

Patients with APDS on long-term treatment with leniolisib.

Anticipated risk/consequence of the missing information:

The anticipated risk is considered low based as final data of Study CCDZ173X2201E1 do not result in changes to the known risk profile of Joenja. No long-term risk has been identified to date.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious diarrhoea/colitis Serious hepatotoxicity Serious and opportunistic infections Pneumonitis Severe cutaneous adverse reactions (SCAR) Embryo-foetal toxicity
Missing information	Safety in patients with hepatic impairment
	Long-term safety

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include adverse reaction reporting, periodic reporting, and signal detection. Cumulative reviews of the safety concerns are planned in the PSURs.

III.2 Additional pharmacovigilance activities

- Planned Post-Authorization Effectiveness and Safety Study (SOB1) (LE 4401) to obtain further data on the long-term clinical benefit of leniolisib and the characterisation of the long-term safety profile of leniolisib in patients with APDS.
- In the context of post-authorisation safety and effectiveness data generation, provide yearly updates on any new information collected concerning the important potential risks and the use of haematopoietic stem cell transplantation (HSCT) in patients treated with leniolisib.
- Ongoing Hepatic impairment study (LE 6101) to assess the impact of moderate and severe hepatic impairment on the pharmacokinetics of leniolisib.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study ***Status***	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
SOB1 (LE 4401) *Planned*	Efficacy objectives are: • To obtain real-world evidence concerning the long-term efficacy of leniolisib in patients with APDS • To provide further evidence of the long-term efficacy of leniolisib in APDS as measured by a reduction of signs and symptoms of APDS	Long-term safety and important potential risks: • Serious colitis/diarrhoea • Serious hepatotoxicity • Serious and opportunistic infections • Pneumonitis	Protocol submission	V0.1 on 10-Oct-2023 (D180 response) V0.2 on 19-Dec-2023 (2nd D180 response) V0.3 on 12-Apr-2024 (3rd D180 response) Final protocol to be

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study ***Status***	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
	Safety objectives are: • To obtain real-world evidence concerning the long-term safety of leniolisib in patients with APDS • To characterise or invalidate the important potential risks of.: o Serious colitis/diarrhoea o Serious hepatotoxicity o Serious and opportunistic infections o Pneumonitis o SCARs o Embryo-foetal toxicity • To evaluate the risks safety of leniolisib used in a patient population for which safety information is limited or missing (e.g., paediatric and geriatric age groups, patients with hepatic impairment and co-medication with mTOR inhibitors) • To assess patterns of drug utilisation that add knowledge regarding the safety of the medicinal product (e.g., collection of information on indication, off-label use, dosage, co-medication, or medication errors in clinical practice that may influence safety, as well as an estimate of the public health impact of any safety concern) • To assess the incidence and causes of death • To assess the impact on fertility, if applicable • To assess pregnancy outcomes if applicable	• SCARs • Embryo-foetal toxicity	Progress reports Final report	submitted within 3 months after EC Decision Yearly updates and progress status within Annual Assessment 1 year after study completion (10 years follow-up).
SOB2	To update annually the regulators on any new information concerning the safety and efficacy. To characterise or invalidate the important potential risks of:	• Serious colitis/diarrhoea • Serious hepatotoxicity • Serious and opportunistic	Yearly reports	Yearly updates after approval of the marketing authorisation application (within

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study *Status*	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	▪ Serious colitis/diarrhoea ▪ Serious hepatotoxicity ▪ Serious and opportunistic infections ▪ Pneumonitis ▪ SCARs ▪ Embryo-foetal toxicity Use of haematopoietic stem cell transplantation (HSCT) will be systematically collected in the context of post-authorisation safety and effectiveness data generation. Specifically, information on HSCT will include, where available: ▪ Whether HSCT was performed (yes/no) ▪ Timing of HSCT in relation to leniolisib treatment (during or after treatment discontinuation) ▪ Reason for HSCT (e.g., disease progression, lack of efficacy, other clinical considerations) ▪ Relevant outcomes, including graft status and major complications	infections • Pneumonitis • SCARs • Embryo-foetal toxicity		Annual Assessment)
Category 3 – Required additional pharmacovigilance activities (by the competent authority)				
Hepatic impairment study (LE 6101) *Ongoing*	Primary: To investigate the effect of hepatic impairment on the plasma PK of leniolisib after oral administration, compared to subjects with normal hepatic function. Secondary: To evaluate the safety profile of a single 70 mg oral dose of leniolisib in hepatic impairment patients.	Safety and PK in patients with moderate to severe hepatic impairment	Protocol submission	V1.0 dated 17 Oct 2023 submitted on 19-Dec-2023 (2nd D180 response) V2.0 dated 11 Dec 2023 submitted on 16-Apr-2024 (briefing document clarification meeting 7 May 2025) V2.1 dated 31 Mar

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study ***Status***	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
				2025 (4th D180 LoOIs response) Update in every PSUR Progress report June 2026 Final report

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study ***Status***	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due date**
Efficacy studies which are conditions of the marketing authorisation				
N/A				
Efficacy studies which are Specific Obligations in the contact of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
N/A				

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

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious diarrhoea/colitis	Routine risk communication: *SmPC Section 4.4, PL Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Information on these important potential risks is included in SmPC Section 4.4. and PL Section 2.* Other routine risk minimization measures beyond the Product Information: *None.*
Serious hepatotoxicity	Routine risk communication: *SmPC Section 4.4, PL Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Information on these important potential risks is included in SmPC Section 4.4. and PL Section 2.* Other routine risk minimization measures beyond the Product Information: *None.*
Serious and opportunistic infections	Routine risk communication: *SmPC Section 4.4, PL Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Information on these important potential risks is included in SmPC Section 4.4. and PL Section 2.* Other routine risk minimization measures beyond the Product Information: *None.*

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Pneumonitis	Routine risk communication: *SmPC Section 4.4, PL Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Information on these important potential risks is included in SmPC Section 4.4. and PL Section 2.* Other routine risk minimization measures beyond the Product Information: *None.*
Severe cutaneous adverse reactions (SCAR)	Routine risk communication: *SmPC Section 4.4, PL Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Information on these important potential risks is included in SmPC Section 4.4. and PL Section 2* Other routine risk minimization measures beyond the Product Information: *None.*
Embryo-foetal toxicity	Routine risk communication: *SmPC Section 4.2, 4.4, and 4.6, PL Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Instruction for women of childbearing potential/contraception in females is included in SmPC Sections 4.2, 4.4, and 4.6, PL Section 2.* Other routine risk minimization measures beyond the Product Information: *None.*

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Safety in patients with hepatic impairment	Routine risk communication: *SmPC Section 4.2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for patients with moderate to severe hepatic impairment is included in SmPC Section 4.2.* Other routine risk minimisation measures beyond the Product Information: *None.*
Long-term safety	Routine risk communication: *None.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None.* Other routine risk minimization measures beyond the Product Information: *None.*

V.2 Additional risk minimisation measures

Not applicable.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Serious diarrhoea/colitis	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date: 1 year after study completion (10 years follow-up)* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Serious hepatotoxicity	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Serious and opportunistic infections	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Pneumonitis	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
SCAR	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Embryo-foetal toxicity	Routine risk minimisation measure: *Instruction for women of childbearing potential/contraception in females is included in SmPC Sections 4.2, 4.4, and 4.6, PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date: 1 year after study completion (10 years follow-up)* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Safety in patients with hepatic impairment	Routine risk minimisation measures: *Recommendation for patients with moderate to severe hepatic impairment is included in SmPC Section 4.2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Hepatic impairment study (LE 6101)* *Final study report due date: 2026.*

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimization measures: *None* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting, signal detection: *None* Additional pharmacovigilance activities: *SOB1 (LE 4401)* *Final study report due date: 1 year after study completion (10 years follow-up).* *SOB2 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Joenja (Leniolisib)

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

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

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

I. The medicine and what it is used for

Joenja is authorised for the treatment of activated PI3Kδ syndrome (APDS) in adult and adolescents aged 12 years and older weighing 45 kg or more (see SmPC for the full indication). It contains leniolisib as the active substance and it is given orally as one tablet of 70 mg twice daily approximately 12 hours apart, with or without food.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Joenja, together with measures to minimize such risks and the proposed studies for learning more about Joenja'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 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 the case of Joenja, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of Joenja are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Joenja. 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).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Serious diarrhoea/colitis
	Serious hepatotoxicity
	Serious and opportunistic infections
	Pneumonitis
	Severe cutaneous adverse events (SCARs)
	Embryo-foetal toxicity
Missing information	Safety in patients with hepatic impairment
	Long-term safety

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important potential risk: Serious diarrhoea/colitis	
Evidence for linking these risks to the medicine	Class-effect of PI3K inhibitors
Risk factors and risk groups	No specific risk factors have been identified for serious diarrhoea/colitis. It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these class effects than the partial inhibition needed for restoring normal immune function in patients with APDS.
Risk minimisation measures	Routine risk minimisation measure: *Information on these events is included in SmPC Section 4.4. and PL Section 2*
Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Serious hepatotoxicity	
Evidence for linking these risks to the medicine	Class-effect of PI3K inhibitors
Risk factors and risk groups	No specific risk factors have been identified for Serious hepatotoxicity. It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these class effects than the partial inhibition needed for restoring normal immune function in patients with APDS.
Risk minimisation measures	Routine risk minimisation measure: *Information on these events is included in SmPC Section 4.4. and PL Section 2*
Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Serious and opportunistic infections	
Evidence for linking these risks to the medicine	Class-effect of PI3K inhibitors
Risk factors and risk groups	Pre-existing lung diseases, like COPD, bronchiectasis and asthma and smoking have been associated with an increased risk of PJP and bacterial pneumonia (Cuneo, 2019). It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these class effects than the partial inhibition needed for restoring normal immune function in patients with APDS.
Risk minimisation measures	Routine risk minimisation measure: *Information on these events is included in SmPC Section 4.4. and PL Section 2*
Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Pneumonitis	
Evidence for linking these risks to the medicine	Class-effect of PI3K inhibitors

Risk factors and risk groups	No specific risk factors have been identified for pneumonitis. It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these class effects than the partial inhibition needed for restoring normal immune function in patients with APDS.
Risk minimisation measures	Routine risk minimisation measure: *Information on these events is included in SmPC Section 4.4. and PL Section 2*
Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Severe cutaneous adverse events (SCAR)	
Evidence for linking these risks to the medicine	Class-effect of PI3K inhibitors
Risk factors and risk groups	No specific risk factors have been identified for SCAR. It is plausible that complete inhibition of PI3K pathway in oncology indications gives more rise to these class effects than the partial inhibition needed for restoring normal immune function in patients with APDS.
Risk minimisation measures	Routine risk minimisation measure: *Information on these events is included in SmPC Section 4.4. and PL Section 2*
Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Class-effect of PI3K inhibitors Microphthalmia at high doses in rats and rabbits in embryofoetal development studies.
Risk factors and risk groups	Women of childbearing potential
Risk minimisation measures	Routine risk minimisation measure: *Instruction for women of childbearing potential/contraception in females is included in SmPC Sections 4.2, 4.4, and 4.6, PL Section 2*

Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Safety in patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measure: *Recommendation for patients with moderate to severe hepatic impairment is included in SmPC Section 4.2.*
Additional pharmacovigilance activities	*Hepatic impairment study* See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Long-term safety	
Risk minimisation measures	As long-term data (both nonclinical and clinical) becomes available, the Applicant will assess the data in the context of the labelling and propose any revisions to the labelling as appropriate.
Additional pharmacovigilance activities	SOB1 See Section II.C of this summary for an overview of the post-authorisation development plan. SOB2 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Study title: A real-world, open-label, non-randomized, non-interventional, post-authorization efficacy and safety study to evaluate the long-term efficacy, safety and tolerability of JOENJA (leniolisib) in patients with APDS (Activated phosphoinositide 3-kinase delta syndrome)

Short title: SOB1

Study number: LE 4401

Purpose of the study: The research question addresses the long-term clinical benefit of leniolisib and the characterization of the long-term safety profile and the primary objective is to obtain real-world evidence concerning the long-term efficacy and safety of leniolisib in patients with APDS.

Study title: Specific Obligation required by regulators for annual reporting

Short title: SOB2

Purpose of the study: To update annually the regulators on any new information concerning the safety and efficacy including:

- Important potential risks:
  - Serious colitis/diarrhoea
  - Serious hepatotoxicity
  - Serious and opportunistic infections
  - Pneumonitis
  - SCAR
  - Embryo-foetal toxicity
- Updates on any new information collected concerning the use of haematopoietic stem cell transplantation (HSCT)

II.C.2 Other studies in post-authorisation development plan

Short title: Hepatic impairment study (ongoing)

Study number: LE 6101

Purpose of the study: To obtain information on the leniolisib exposure in patients with moderate to severe hepatic impairment.

PART VII: ANNEXES

Table of contents

Annex 4 Specific adverse drug reaction follow-up forms

No specific adverse drug reaction follow-up forms are in place for Joenja.

Annex 6 Details of proposed additional risk minimisation activities

No additional risk minimisation activities are proposed for Joenja.

Annex 7 Other supporting data (including referenced material)

- Angulo I, Vadas O, Garcon F, Banham-Hall E, Plagnol V, et al. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. Science 2013;342(6160):866.
- Bousfiha A, Jeddane L, Moundir A, Poli M, Aksentijevich I et al. The 2024 update of IUIS phenotypic classification of human inborn errors of immunity. Journal of Human Immunity, 2025 1(1), e20250002.
- Bloomfield M, Klocperk A, Zachova R, Milota T, Kanderova V, et al. Natural Course of Activated Phosphoinositide 3-Kinase Delta Syndrome in Childhood and Adolescence. Front Pediatr. 2021;9:697706.
- Boyle J, Buckley R. Population Prevalence of Diagnosed Primary Immunodeficiency Diseases in the United States. J Clin Immunol 2007;27: 497-502.
- Coulter T, Chandra A, Bacon C, Babar J, Curtis J, et al. Clinical Spectrum and Features of Activated Phosphoinositide 3-kinase delta Syndrome: a Large Patient Cohort Study. J Allergy Clin Immunol 2017;139(2):597–606.e4.
- Coulter T, Cant A. The Treatment of Activated PI3Kδ Syndrome. Front Immunol. 2018;9:2043
- Coutré S, Barrientos J, Brown J, de Vos S, Furman R, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma. 2015;56(10):2779-86.
- Cuneo A, Barosi G, Danesi R, Fagiuoli S, Ghia P, et al. Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: A multidisciplinary position paper. Hematol Oncol. 2019;37(1):3-14.
- Diaz N, Juarez M, Cancrini C, Heeg M, Soler-Palacín P, et al. Seletalisib for Activated PI3Kδ Syndromes: Open-Label Phase 1b and Extension Studies. J Immunol. 2020;205(11)2979-2987.
- Eades-Perner A, Gathmann B, Knerr V, Guzman D, Veit D. The European Internet-based Patient and Research Database for Primary Immunodeficiencies: Results 2004–06. Clin Exp 2007;147: 306-12.
- EU/3/20/2339: Orphan designation for the treatment of APDS
- Eurostat Regional Yearbook 2020. European Union. 2020 July. Eurostat 2023. How many children were born in the EU in 2021? - Products Eurostat News - Eurostat (europa.eu)
- Ewertowska M, Grześk E, Urbańczyk A, Dąbrowska A, Bąbol-Pokora K, et al. Activated phosphoinositide 3-kinase delta syndrome 1 and 2 (APDS 1 and APDS 2): similarities and differences based on clinical presentation in two boys. Allergy Asthma Clin Immunol. 2020;16:22.
- FDA Briefing document PI3K inhibitors in hematologic malignancies, 2022. https://www.fda.gov/media/157762/download. Last accessed 18Mar2024.
- Flinn I, Cherry M, Maris M, Matous J, Berdeja J, Patel M. Combination trial of duvelisib (IPI-145) with rituximab or bendamustine/rituximab in patients with non-Hodgkin lymphoma or chronic lymphocytic leukemia. Am J Hematol. 2019 Dec;94(12):1325-1334.
- Gabriel J, Kapila A, Gonzalez-Estrada A. A Severe Case of Cutaneous Adverse Drug Reaction Secondary to a Novice Drug: Idelalisib. J Investig Med High Impact Case Rep. 2017 May 24;5(2):2324709617711463.
- Hanlon A, Brander D. Managing toxicities of phosphatidylinositol-3-kinase (PI3K) inhibitors. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):346-356.
- Hanson J, Bonnen P. Systematic review of mortality and survival rates for APDS. Clin Exp Med. 2024;24(1):17. Clin Exp Med. 2024;24(1):17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10821986/pdf/10238_2023_Article_1259.pdf
- Helmer E, Watling M, Jones E, Tytgat D, Jones M, et al. First-in-human studies of seletalisib, an orally bioavailable small-molecule PI3Kδ inhibitor for the treatment of immune and inflammatory

diseases. Eur J Clin Pharmacol. 2017;73(5):581-591.

- Hoegenauer K, Soldermann N, Zécri F, Strang R, Graveleau N, et al. Discovery of CDZ173 (Leniolisib), Representing a Structurally Novel Class of PI3K Delta-Selective Inhibitors. ACS Med Chem Lett. 2017;8(9):975-980.
- Hus I, Puła B, Robak T. PI3K Inhibitors for the Treatment of Chronic Lymphocytic Leukemia: Current Status and Future Perspectives. Cancers (Basel). 2022 Mar 18;14(6):1571.
- Jamee M. Clinical, Immunological, and Genetic Features in Patients with Activated PI3Kdelta Syndrome (APDS): a Systematic Review. Clin Rev Allergy Immunol 2020;59:323-333.
- JOENJA US PI. Prescribing information. FDA 2025. Current: Package Insert & Patient Product Information
- Jou S, Chien Y, Yang Y, Wang T, Shyur S, et al. Identification of Varitation in the Human Phosphoinositide 3-kinase p110delta Gene in Children with Primary B-cell Immunodeficiency of Unknown Aetiology. Int J Immunogenet 2006;33(5): 361-369.
- Lucas C, Chandra A, Nejentsev S, Condliffe A, Okkenhaug K. PI3Kdelta and Primary Immunodeficiencies. Nat Rev Immunol 2016;16(11): 702-714.
- Maccari M, Wolkewitz M, Schwab C, Lorenzini T, Leiding J, et al. Activated phosphoinositide 3-kinase δ syndrome: Update from the ESID Registry and comparison with other autoimmune-lymphoproliferative inborn errors of immunity. J Allergy Clin Immunol 2023;28:S0091-6749(23)00812-6.
- Nademi Z, Slatter M, Dvorak C, Neven B, Fischer A, et al. Hematopoietic Stem Cell Transplant in Patients with Activated PI3K delta Syndrome. J Allery Clin Immunol 2017;139(3):1046-9.
- Okano T, Imai K, Tsujita Y, Mitsuiki N, Yoshida K, et al. Hematopoietic Stem Cell Transplantation for Progressive Combined Immunodeficiency and Lymphoproliferation in Patients with Activated Phosphatidylinositol-3-OH Kinase Delta Syndrome Type 1. J Allergy Clin Immunol 2019;143(1): 266-275.
- Pilmis B, Kherabi Y, Huriez P, Zahar J, Mokart D. Infectious Complications of Targeted Therapies for Solid Cancers or Leukemias/Lymphomas. Cancers (Basel). 2023;27;15(7):1989.
- Rao V, Webster S, Šedivá A, Plebani A, Schuetz C, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome. Blood. 2023;2;141(9):971-983.
- Rohrbacher L, Brauchle B, Ogrinc Wagner A, von Bergwelt-Baildon M, Bücklein V, Subklewe M. The PI3K∂-Selective Inhibitor Idelalisib Induces T- and NK-Cell Dysfunction Independently of B-Cell Malignancy-Associated Immunosuppression. Front Immunol. 2021 Mar 15;12:608625.
- Smolewski P, Rydygier D. Efficacy and Safety of Idelalisib for the Treatment of Indolent B-cell Malignancies. Expert Opin Pharmacother 2020: 1-12.
- Sobh A, Bonilla F. Vaccination in Primary Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2016;4(6):1066-1075.
- Tangye S, Bier J, Lau A, Nguyen T, Uzel G, et al. Immune Dysregulation and Disease Pathogenesis due to Activating Mutations PIK3CD-the Goldilocks' Effect. J Clin Immunol 2019;39(2): 148-158.
- Thaventhiran J, Lango Allen H, Burren O, Rae W, Greene D, et al. Whole-genome sequencing of a sporadic primary immunodeficiency cohort. Nature 2020; 583(7814): 90-95.
- ZYDELIG EU SmPC. https://www.ema.europa.eu/en/documents/product-information/zydelig-epar-product-information_en.pdf