30 March 2026
EMA/OD/0000117371
EMADOC-1700519818-3047528
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Joenja (leniolisib)
Treatment of activated phosphoinositide 3-kinase delta syndrome
EU/3/20/2339

Sponsor: Pharming Technologies B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Leniolisib
Other name(s)	-
International Non-Proprietary Name	Leniolisib
Tradename	Joenja
Orphan condition	Treatment of activated phosphoinositide 3-kinase delta syndrome
Sponsor's details:	Pharming Technologies B.V. Darwinweg 24 2333 CR Leiden Zuid-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharming Group N.V.
COMP opinion	18 September 2020
EC decision	19 October 2020
EC registration number	EU/3/20/2339
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pharming Group N.V. to Pharming Technologies B.V. – EC decision of 7 April 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Armando Genazzani
Applicant	Pharming Technologies B.V.
Application submission	4 October 2022
Procedure start	27 October 2022
Procedure number	EMA/H/C/005927
Invented name	Joenja
Therapeutic indication	Joenja 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. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Joenja
CHMP opinion	26 March 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Cécile Dop
Sponsor's report submission	14 November 2022
COMP discussion	7-9 November 2023 and 17-19 February 2026
COMP opinion (adoption via written procedure)	30 March 2026

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2022 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing leniolisib was considered justified based on preliminary clinical observations showing restoration of lymphocyte population frequencies and reduction of spleen and lymph nodes sizes;
- the condition is life-threatening and chronically debilitating due to recurrent respiratory infections, leading to bronchiectasis, progressive lymphopenia, and defective antibody production;
- the condition was estimated to be affecting approximately 0.01 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing leniolisib as an orphan medicinal product for the orphan condition: treatment of activated phosphoinositide 3-kinase delta syndrome".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Activated PI3 kinase delta syndrome (APDS) is a primary immunodeficiency caused by dominant mutations that increase activity of phosphoinositide-3-kinase δ (PI3Kδ). APDS can be caused by mutations in the PIK3CD gene that encodes PI3Kδ catalytic subunit p110δ (APDS1) or mutations in the PIK3R1 gene that encodes regulatory subunit p85α (APDS2) (Michalovich Front Immunol. 2018 Feb 27;9:369).

These mutations result in the hyperactivation of the PI3K/AKT/mTOR/S6K signalling pathways and combined immunodeficiency. In a cohort of patients described in 2017, the most common clinical

manifestations are described (Coulter et al, J Allergy Clin Immunol 2017 139:2:597): The authors note recurrent sinopulmonary infections (98%) and nonneoplastic lymphoproliferation (75%), often present from childhood. Other significant complications included herpesvirus infections, autoinflammatory disease, and lymphoma. Unexpectedly, neurodevelopmental delay occurred in 19% of the cohort.

The approved therapeutic indication "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" falls within the scope of the designated orphan condition "treatment of activated phosphoinositide 3-kinase delta syndrome".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The COMP has previously considered that the condition is chronically debilitating due to recurrent respiratory infections, leading to bronchiectasis, progressive lymphopenia, and defective antibody production. In the more severe forms this leads to death.

The sponsor notes that the clinical profile of patients with APDS varies in spectrum from mildest forms to severe life-threatening manifestations (Singh et al 2019). In a systematic review of 243 patients, 103 patients had known life status information. 14 of those 103 patients (12%) were described to be deceased (Jamee et al 2019). Malignancies (e.g., lymphoma, and acute myeloid leukaemia), cardiopulmonary arrest, bowel perforation, septic shock, multiple organ failure, and pulmonary haemorrhage were the reported causes of death.

Susceptibility to (chronic) viral infections, most notably Epstein Barr-virus (EBV), which may contribute to the preexisting tumour risk (Carpier 2018, Jamee et al 2019).

Review of literature published since the original application has revealed a number of further associated risks such as autoimmune thyroiditis (Bloomfield et al 2021), poor response to vaccines (Bloomfield et al 2021), respiratory infections (Oh et al 2021, Qiu et al 2022), herpesvirus infections (Oh et al 2021), bronchiectasis (Oh et al 2021), and developmental delay (Oh et al 2021).

The chronically debilitating and life-threatening nature of the condition has been adequately justified.

Number of people affected or at risk

The sponsor's approach to estimating the prevalence of activated PI3K delta syndrome (APDS) is based on the use of multiple heterogeneous data sources, combining registry data, published case series, extrapolations from related diseases, and reference databases. At the time of initial orphan designation in 2020, the estimate of approximately 0.01 per 10,000 persons in the European Union was derived from a range of calculations rather than a single epidemiological study, reflecting the rarity of the condition and the absence of large population-based datasets.

For the purpose of the maintenance of the orphan designation, the sponsor initially compiled prevalence estimates from several categories of evidence. These include data from Orphanet, which reports a prevalence of less than 1 in 1,000,000 (<0.01 per 10,000) in Europe (Orphanet, Orpha number 397596). More relevant, registry-based approaches were used, whereby the number of known APDS patients was divided by the population of a defined region. For example, 77 patients identified in the European APDS Registry (Maccari et al., 2018) over a European population of approximately 519.2

million yielded an estimated prevalence of 0.0015 per 10,000. Similarly, national-level data, such as 3 patients identified in Germany in 2017 (El-Helou et al., 2019 Supplement) over a population of 82.5 million, resulted in a lower estimate of 0.00036 per 10,000. A global estimate based on 243 reported cases (Jamee et al., 2019) over a world population of 7.7 billion produced a prevalence of 0.00032 per 10,000.

A second methodological pillar used by the sponsor involves indirect estimation based on the proportion of APDS cases identified within populations of patients diagnosed with related immunological disorders, particularly primary immunodeficiencies (PID). For instance, in a cohort of 669 PID patients, 5 were found to have APDS following genetic testing (Elgizouli et al., 2016). Using the European Society for Immunodeficiencies (ESID) estimate of maximum PID prevalence (0.5 per 10,000), this translates to an APDS prevalence of approximately 0.0037 per 10,000. A similar approach using ESID registry data (3 APDS cases among 2,453 PID patients; El-Helou et al., 2019) yielded an estimate of 0.0006 per 10,000 in Germany. Other enriched cohorts, such as a UK study with familial susceptibility to infections (Angulo et al., 2013), produced higher estimates (0.038 per 10,000).

The sponsor also considered misdiagnosis within clinically overlapping conditions, particularly common variable immunodeficiency (CVID). Based on literature indicating that 0.64% to 3.2% of CVID cases may be attributable to mutations in PIK3CD or PIK3R1 (Bogaert et al., 2016; Maffucci et al., 2016; Aggarwal et al., 2019), and assuming a maximum CVID prevalence of 0.9 per 10,000, an upper estimate of 0.0288 per 10,000 was derived. This was further adjusted using evidence that approximately 15% of APDS patients were initially misdiagnosed as CVID (Jamee et al., 2019), leading to a corrected theoretical maximum estimate of 0.19 per 10,000 worldwide. The sponsor presents this as a conservative upper bound rather than a realistic estimate.

More recent data from the ESID APDS Registry (Newsletter 3, January 2021) were also incorporated. The registry reports 175 genetically confirmed APDS1/2 patients (level 1) and 130 patients in a more detailed registry (level 3). Using the ESID-defined European population of approximately 845 million, the sponsor calculated a prevalence of 0.002 per 10,000 based on the higher patient count.

Finally, the sponsor notes that subsequent literature does not challenge the original estimate. A review by Bloomfield et al. (2021) states that over 200 APDS patients have been reported worldwide since the condition was first described in 2013, supporting the conclusion that APDS remains a rare disorder.

Overall, the sponsor's strategy relies on synthesizing multiple complementary estimation approaches, each with inherent limitations, including underdiagnosis, reporting bias, and variability in diagnostic practices. Despite variability across methods, the convergence of estimates - generally in the range of 0.0003 to 0.0037 per 10,000, with higher values representing theoretical maxima - supports the sponsor's conclusion that a prevalence of approximately 0.01 per 10,000 in the EU is a reasonable and conservative estimate. The methodology and figure proposed were considered to be acceptable by COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

No additional authorised medicinal products have been identified by the sponsor since the time of designation. The only potentially curative non-medicinal option remains allogeneic haematopoietic stem cell transplantation (HSCT). Overall, management therefore remains largely supportive and consistent with the situation previously described.

Antimicrobial prophylaxis
Antimicrobial prophylaxis is routinely used to reduce the frequency and severity of infections. While sufficient as monotherapy in a minority of patients, it is most commonly administered in combination with other supportive measures, such as immunoglobulin replacement therapy.

Immunoglobulin replacement therapy (IRT)
IRT, administered intravenously or subcutaneously, is a cornerstone of management for patients with antibody deficiency. As many patients with APDS present with reduced IgG and IgA levels in the context of normal or elevated IgM, IRT is often effective in preventing recurrent infections. However, it does not address the underlying immune dysregulation or lymphoproliferative manifestations of the disease.

Haematopoietic stem cell transplantation (HSCT)
Allogeneic HSCT represents the only potentially curative intervention and has been associated with resolution of pre-transplant clinical manifestations (Coulter et al., 2018). However, it carries significant risks and is generally reserved for patients with severe, life-threatening disease who are refractory to other therapeutic interventions.

Immunosuppressive therapies
Immunosuppressive agents are used to manage autoimmune and inflammatory complications. In a review of 243 patients with APDS (Jamee et al., 2019), approximately one third experienced autoimmune manifestations. Reported treatments included corticosteroids, sirolimus (rapamycin), rituximab, tacrolimus, mycophenolate mofetil, azathioprine, and cyclosporine. Inflammatory complications were managed with regimens such as prednisolone in combination with mesalazine (one patient) or rituximab (five patients) (Jamee et al., 2019).

mTOR inhibitors
mTOR inhibitors, such as sirolimus, are frequently used to mitigate benign lymphoproliferative manifestations. Registry data analysis (Maccari et al., 2018) indicated complete responses in 8 of 25 patients and partial responses in 11 of 25 patients treated for lymphoproliferation. Nevertheless, responses were variable and not uniformly sustained.

In summary, treatment remains predominantly supportive and symptom-directed, with HSCT reserved for selected severe cases. In this context, the COMP has considered that no satisfactory authorised methods of treatment are available that would require a justification of significant benefit.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 30 March 2026

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of activated phosphoinositide 3-kinase delta syndrome (APDS) (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.01 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to recurrent respiratory infections, leading to bronchiectasis, progressive lymphopenia, and defective antibody production;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Joenja, leniolisib for treatment of activated phosphoinositide 3-kinase delta syndrome (EU/3/20/2339) is not removed from the Community Register of Orphan Medicinal Products.