SMC2836

leniolisib film-coated tablet (Joenja®)

Pharming Group N.V.

07 November 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

Indication under review: Treatment of activated phosphoinositide 3-kinase delta (PI3K-delta) syndrome (APDS) in adult and paediatric patients 12 years of age and older.

Key points:

- Activated phosphoinositide 3-kinase delta (PI3K-delta) syndrome (APDS) is a rare genetic disorder with over activation of PI3K-delta, which presents as immune dysregulation, with chronic infections, lymphoproliferation, autoimmunity and reduced life expectancy. No other medicines are licensed for the treatment of APDS and there is unmet need for targeted therapies.
- In a double-blind study, 12 weeks of leniolisib, compared with placebo, significantly improved the size of index lesions and percentage of naïve B cells per total B cells. Although not clinical outcomes, these are relevant to how APDS affects the immune system.
- There is a lack of direct comparative data beyond 12 weeks and data on clinical outcomes.
- There was no difference compared with placebo over 12 weeks for quality of life outcomes but there appeared to be improvement in general health compared with baseline over the longer-term extension study and an increase in work or school days.
- A model-based health economic evaluation indicated that leniolisib is associated with increased costs compared with current clinical management. However, treatment with leniolisib was also predicted to increase health outcomes, as measured by quality adjusted life years. The economic analysis contained some areas of uncertainty, which may have impacted on results. The main identified areas of uncertainty were the handling of treatment waning, post-discontinuation risks, overall survival modelling, modelling of utilities and sensitivity analysis.

Chair
Scottish Medicines Consortium

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1. Clinical context

1.1. Background

Leniolisib is an inhibitor of phosphoinositide 3-kinase delta (PI3K-delta) that reduces the overactivity of this enzyme, which characterises activated PI3K-delta syndrome (APDS). This may resolve the clinical symptoms associated with overactivation of PI3K-delta. Leniolisib is the first medicine licensed for treatment of APDS and can be taken orally by patients at least 12 years of age who weigh at least 45kg, at a dose of 70 mg twice daily.[1]

1.2. Nature of condition

The rare genetic disorder, APDS, has an estimated prevalence of between 1 and 2 per million. It presents with immune dysfunction and immune deficiency resulting from over activation of the PI3K-delta enzyme, that has a role in T and B cells regulation. It is caused by pathogenic autosomal dominant variants in one of two independent genes. APDS1 results from gain of function variants in the PIK3CD gene, while APDS2 is caused by loss of function variants in PIK3R1. Patients have a higher-than-normal proportion of transitional B cells with a reduced proportion of naïve B cells and fewer switched memory B cells. They have impaired switching of immunoglobulin (Ig) class, resulting in reduced levels of higher affinity antibodies such as IgG and IgA, and elevated levels of lower affinity IgM. They also have more senescent and exhausted effector T cells, with fewer naïve and functional memory T cells. Overall, the immune dysfunction and immune deficiency that characterises APDS underpins many of the clinical symptoms.[2-5]

Patients usually have severe recurrent infections from their first year of life, commonly sinopulmonary. They have a predisposition to bacterial infections and viral infections, including chronic non-resolving herpes virus infections such as Epstein-Barr virus, cytomegalovirus and herpes simplex virus. Lymphoproliferation is characteristic of the condition and can present as lymphoid hyperplasia, lymphadenopathy, splenomegaly, or hepatomegaly, and may potentially involve the airways and gastrointestinal tract, with increased susceptibility to develop to malignant lymphoma. Many patients suffer autoimmune conditions, including haemolytic anaemia, pancytopenia, and thrombocytopenia. Other symptoms included bronchiectasis, enteropathy and deafness, with organ damage accumulating over time in this progressive condition.[2-4] As APDS was first described in 2013,[4] data on mortality and long-term outcomes are developing. Life expectancy appears reduced, with the most common cause of death being lymphoma, followed by complications of haematopoietic stem cell transplantation (HSCT).[2]

The patient's quality of life is affected by the number and type of heterogeneous symptoms they suffer and how these impact their ability to undertake daily activities of living. The chronic progressive nature of this condition may impact the patient's mental health.[6]

No other medicines are licensed specifically for APDS. Treatment has been symptomatic, including antibiotics and immunoglobulin replacement therapy (IRT) for infections and immune

dysregulation. To mitigate autoimmunity and lymphoproliferation, immunosuppressive agents are used, including corticosteroids, rituximab, tacrolimus, and mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus, which inhibits mTOR downstream of PI3K. A minority of patients have undergone HSCT despite its substantial risk of adverse complications, including death.[2-4] However, none of these treatments targets the underlying cause of APDS; they may have limited efficacy and substantial adverse effects. There is an unmet need for targeted therapies with improved efficacy in treating APDS and acceptable tolerability.

Clinical experts consulted by SMC considered that leniolisib fills an unmet need in this therapeutic area, namely as the first licensed medicine and targeted therapy for the treatment of APDS.

2. Impact of new technology

Comparative efficacy

The main evidence is from the placebo-controlled Part II of Study 2201. This is supported by the single-arm dose-escalation phase, Part I of Study 2201, and extension, Study 2201E1.[4, 7]

Table 2.1 Overview of relevant study.[4, 7]

Criteria	Study 2201 Part II
Study design	International, double-blind, phase III
Eligible patients	Patients, 12 to 75 years old (weighing ≥ 45kg), with APDS-associated genetic PI3K delta mutation in PIK3CD or PIK3R and ≥1 measurable nodal lesion on CT or MRI. Nodal and/or extra nodal lymphoproliferation and clinical symptoms of APDS such repeated oto-sino-pulmonary infections and/or organ dysfunction.
Treatments	Leniolisib 70 mg orally twice daily or placebo for 12 weeks.
Randomisation	Randomised 2:1 to leniolisib or placebo.
Co-primary outcomes	Change from baseline to day 85 in $\log_{10}$ transformed sum of product of diameters in the index lesions selected per Cheson methodology from MRI/CT. Change from baseline day 85 in percentage of naïve B cells out of total B cells.
Secondary outcomes	Change from baseline to day 85 in: volume of index and measurable non-index lesions and spleen; bi-dimensional size of spleen at Day 85; SF-36 and WPAI-CIQ; PGA and PtGA; biochemical variables. Single-dose pharmacokinetic parameters.
Statistical analysis	The pharmacodynamics analysis set included all patients who received any study drug with no protocol deviations and with relevant impact on endpoints. Analysis of the lesion primary outcome excluded patients with no nodes at day 85. Analysis of the B cell primary outcome only included patients with <48% naïve B cells at baseline. Multiplicity was controlled across the primary outcomes as both were required to be significant. Secondary outcomes were not controlled for multiplicity.

Abbreviations: APDS = activated phosphoinositide 3-kinase delta syndrome; CT = computed tomography; MRI = magnetic resonance imaging; PGA = physician global assessment; PI3K = phosphoinositide 3-kinase delta; PtGA = patient global assessment; SF-36 = short-form 36 questionnaire; WPAI-CIQ = Work Productivity Activity Impairment Classroom Impairment Questionnaire.

At the primary analysis, leniolisib significantly improved both co-primary outcomes compared with placebo and there appeared to be benefits with leniolisib in some secondary outcomes that

assessed the size of lymph nodes and spleen, plus T cell and immunoglobulin levels. Selected results are detailed in Table 2.2.[4, 7]

Table 2.2: Results of Study 2201 Part II.[4, 7]

Least Square Mean Change from baseline to Day 85	Leniolisib	Placebo	Difference (95% CI), p-value
Co-primary outcomes			
Log_{10} SPD of index lesions[A]	-0.27	-0.02	-0.25 (-0.38 to -0.12) p<0.001
Naïve B cells per total B cells[B]	37.39	0.09	37.30 (24.06 to 50.54) p<0.001
Secondary outcomes			
Log_{10} volume index lesions[A]	-2.08	-1.10	-0.97 (-2.74 to 0.79)
Log_{10} volume non-index lesions[C]	-1.63	0.08	-1.71 (-2.77 to -0.64)
Spleen bidimensional size[D]	-1,428	-77	-1,350 (-2,409 to -291)
Spleen volume[D]	-182,799	3,562	-186,361 (-296,547 to -76,175)

Abbreviations: CI = confidence interval SPD = sum of product of diameters.
A = assessed in 18 and 8 patients within the leniolisib and placebo group, respectively, with nodes at day 85; B = assessed in 8 and 5 patients within the leniolisib and placebo groups, respectively, with less than 48% naïve B cells at baseline; C = assessed in 16 and 8 patients within the leniolisib and placebo groups, respectively, with non-index lesions; D = assessed in 19 and 8 patients within the leniolisib and placebo groups, respectively, which comprised the pharmacodynamic set (that is, had no protocol violations).

The open-label extension study included 6 and 29 patients who participated in Part I or II of Study 2201, respectively, and 2 patients who had previously received a PI3K-delta inhibitor but not leniolisib. All patients received open-label leniolisib 70 mg orally twice daily and were to be followed for up to 7 years. In interim analyses at data cut-offs 13 December 2021 and 13 March 2023 median duration of leniolisib treatment was 102 and 155 weeks, respectively. Although the study was primarily designed to assess safety, the secondary and exploratory efficacy outcomes indicate that there was a 63% reduction from screening to first open-label extension assessment in mean index lymph node size and a 38% reduction in mean spleen volume. Patients with previous exposure to leniolisib during Part I or II of Study 2201 had a continued reduction in lymphoproliferation. The mean percentage of naïve B cells and transitional B cells came were maintained within normal limits from extension day 84 and percentage of mature B cells increased throughout. At screening, 27 patients were receiving IRT and by the first interim analysis, 6, 3 and 1 patients had 100%, 50% and 30% dose reductions, respectively. At the second interim analysis, there was a non-significant (p=0.08) trend for reduction in IRT use (per 3-month period). Post hoc analysis indicated a reduction of 0.351 in annualised rate of infection with each additional year of leniolisib.[8] The company has advised that the study closed in January 2025 and the clinical study report (CSR) with the final data cut (30 January 2025) is available.

In the double-blind Part II of Study 2201, health related quality of life was assessed using the following questionnaires: short form 36 (SF-36), Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire (WPAI-CIQ), Patient Global Assessment Questionnaire (PtGA), and the Physician's Global Assessment Questionnaire (PGA). There were no substantial differences between the groups in patient and physician global assessments.[4] In the open-label

extension, the mean changes from baseline were generally less than 5-points on the 100-point SF-36 component summaries and scales, except for general health, which improved by 7.2 to 11.04 in analyses from weeks 12 to 208. The WPAI-CIQ scores indicated a general increase from baseline in the hours worked and hours of class throughout the extension study.[9]

*Other data were also assessed but remain confidential.**

There has been a published indirect comparison of patients in the open-label extension Study 2201E1 and patients with APDS included in the European Society for Immunodeficiencies (ESID) registry, detailed in Table 2.3.[5]

Table 2.3: Summary of indirect treatment comparison.[5]

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Design</td><td>Matched adjusted indirect comparison</td></tr>
<tr><td>Population</td><td>Patients with APDS</td></tr>
<tr><td>Comparators</td><td>Standard of care (including antibiotics, immunoglobulin replacement therapy, corticosteroids, immunosuppressants and symptomatic treatments)</td></tr>
<tr><td>Studies included</td><td>Study 2201E1 and European Society for Immunodeficiencies (ESID) registry</td></tr>
<tr><td>Outcomes</td><td>Annual rate of respiratory infection; Annual change in IgM levels</td></tr>
<tr><td>Results</td><td>Results of the indirect treatment comparison
<table>
<tr><th></th><th>Control group (standard of care)</th><th>Treatment group (leniolisib)</th></tr>
<tr><td colspan="3">Annual rate of respiratory tract infections</td></tr>
<tr><td>Number of participants</td><td>62</td><td>37</td></tr>
<tr><td>Annualised rates (95% CI)</td><td>1.34 (0.89 to 2.00)</td><td>0.45 (0.29 to 0.70)</td></tr>
<tr><td>Rate ratio for annualised rates (95% CI)</td><td colspan="2">0.34 (0.19 to 0.59)</td></tr>
<tr><td colspan="3">Change in serum IgM level</td></tr>
<tr><td>Number of participants</td><td>49</td><td>37</td></tr>
<tr><td>Difference in median annualised change in IgM (95% CI)</td><td colspan="2">-1.09 g/L (-1.78 to -0.39, p=0.002)</td></tr>
</table></td></tr>
<tr><td>Company conclusion</td><td>Leniolisib improves the rate of respiratory infection and elevated IgM seen in APDS.</td></tr>
</table>

Abbreviations: APDS = Activated phosphoinositide 3-kinase delta syndrome; CI = confidence interval; IgM = immunoglobulin M.

Comparative safety

A regulatory review concluded that in the leniolisib studies serious adverse events, adverse events leading to discontinuation, and severe or life-threatening adverse events were infrequent, and extended exposure did not indicate any concerning safety signals.[4]

In the double-blind Part II of Study 2201, within the leniolisib and placebo groups, adverse events were reported by 86% (18/21) and 90% (9/10) of patients, respectively; drug-related adverse events by 24% and 30%; non-fatal serious adverse events by 14% and 20%; and fatal adverse events by 0 and 10%.[4]

Adverse events reported by at least 2 patients in Part II of Study 2201, within the leniolisib and placebo groups, respectively, included: headache (24% and 20%), sinusitis (19% and 0), atopic dermatitis (14% and 0), fatigue (10% and 10%), alopecia (10% and 0), back pain (10% and 0), diarrhoea (10% and 0), neck pain (10% and 0), pyrexia (10% and 0), and tachycardia (10% and 0).[4]

In the open-label extension study (at data cut-off 13 December 2021), adverse events were reported by 86% (32/37) of patients and were treatment-related in 14% (5/37). Common adverse events included upper respiratory tract infection (24%), headache (16%), pyrexia (16%), COVID-19 (14%), pharyngitis (11%), respiratory tract infection (11%) and diarrhoea (11%). Serious adverse events were reported by 16% (6/37) but were not considered related to study drug.[8]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- In a double-blind study, 12 weeks of leniolisib, compared with placebo, significantly improved the size of index lesions and percentage of naïve B cells per total B cells.[4, 7] While these are not clinical outcomes, they are based on the pathophysiology of the disease. A regulatory review noted that correction of B cell dysfunction and lymphoproliferation observed in this study are clinically meaningful and would be unlikely to occur spontaneously without intervention.[4]
- The primary outcomes are supported by improvements in secondary outcomes that assessed spleen size and volume, non-index lesion measures of lymphadenopathy, and other immune parameters, such as IgM levels. It was noted that correction of the abnormal immunophenotype associated with APDS would be expected to lead to normalisation of immune function and improvement in clinical sequelae such as fewer infections, autoimmune manifestations, and lymphoproliferative disease.[4]
- Clinical experts consulted by SMC considered that leniolisib is a therapeutic advancement as it is the first medicine licensed for treatment of APDS. It is an inhibitor of the PI3K-delta enzyme, which is overactive in APDS, providing a targeted treatment.[1] Clinical experts considered that the place in therapy of leniolisib is for all patients with APDS.

Key uncertainties:

- There is a lack of direct comparative data beyond 12 weeks and on clinical outcomes. As APDS is a recently recognised disease, first described in 2013, information on its

clinical course and prognosis is developing and there are no clinical outcomes established as standard indicators of benefit in this condition.[4]

- As this is a lifelong condition, the lack of long-term data relating to clinical outcomes, such as organ dysfunction, malignancies, and life expectancy is a limitation.
- Leniolisib may be added to standard of care for APDS. The studies excluded patients receiving immunosuppressive treatments and prohibited use of these medications, which are often included in the standard of care for APDS.[4, 7] However, clinical experts consulted by the company advise that in practice this is likely to reflect the way in which leniolisib would be used in practice. The exclusion of immunosuppressive treatments from the placebo group could potentially mean those patients were undertreated compared with clinical practice and limit the interpretation of relative effectiveness in the key study.
- The indirect comparison of leniolisib study data from the open-label extension Study 2201E1 with ESID data is limited by differences in baseline characteristics that were not matched and that persisted after matching for some variables. There were also differences in methods of collecting and analysing data on the two outcomes (respiratory infection rate and IgM levels). The criteria for inclusion in the open-label extension and registry differed and the comparison was limited by small sample size. Therefore, there is uncertainty around the results and conclusions.[5]

3. Impact beyond direct health benefits and on specialist services

Correction of the enzyme overactivity, which characterises APDS, may be expected to improve the symptom burden and fatigue associated with infection, lymphadenopathy and autoimmune disorders that define this condition. Thus, leniolisib may allow patients to participate more in family life, education, work and socialising, which could mitigate the negative consequence of limitations in these areas that APDS sufferers usually experience. That is, they may avoid delays in child development, including academically and socially, which can be key for adolescents, and they may be able to work and progress their career to a greater extent, providing financially for their family. They would have a reduced requirement for caregiver and societal support. This, together with reduced concerns about catching an infection (which can often lead to social isolation) and progression of APDS to malignancy or the need for HSCT, may improve the patient's mental health.

Patients with APDS often require support from family, due to developmental delays and to manage their condition, for example, to attend healthcare appointments for extended course of drug treatment (such as IRT) or physiotherapy. The unpredictable nature of infections adds to the challenges of the carer and can create difficulties for the family to plan, for example, for holidays. Often, carers are unable to maintain employment, leading to financial difficulties, and they may have less time to spend with their other children. Leniolisib may improve the carer's situation by improving the patient's condition, giving them more self-reliance, and reducing

the need to attend healthcare appointments. This would give the carer more time to work, care for other children and socialise. Together with a reduction in anxiety about the progression of the patient's condition (infection and risk of malignancy or HSCT), this may have a positive impact on the carer's mental health.

Leniolisib may reduce the patient's need for societal help and healthcare. Hospital admissions and clinic visits could potentially be reduced if clinical benefits occurred, particularly relevant for resources that can be limited such as IRT or HSCT. By decreasing the patient's exposure to antibiotics, it may help limit the development of antibiotic-resistant microbes.

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Immunodeficiency UK, which is a registered charity.
- Immunodeficiency UK has received 60.7% pharmaceutical company funding in the past two years, including from the submitting company.
- Living with APDS can have a profound negative impact on the physical and mental health, and quality of life of those affected, their carers, and families. Health problems that have an extreme impact on quality of life include respiratory infections, chronic cough, autoimmune problems, enlarged lymph nodes, gastrointestinal problems, enlarged spleen, and hearing problems.
- Current medicines manage the condition but do not address the underlying dysregulation of the immune system that is seen in APDS, which can result in a higher incidence of lymphoma, autoimmunity, and inflammatory problems.
- Leniolisib is the only targeted pathway-specific medicine available for patients with APDS that helps address the underlying problems of the dysregulated, overactive immune system seen in APDS.
- Patients and carers reported significant health benefits of taking leniolisib, including reducing lymph node size, reducing hospital admissions, improved energy levels, and a reduction in antibiotic use.
- By helping to normalise the immune system in people with APDS, the medicine will help improve long-term health outcomes, rather than them experiencing a progressive deterioration in health. It also has the potential to decrease the chance of developing lymphoma in people with APDS, giving reassurance and hope for the future.

5. Value for money

5.1. Economic case

An economic case was presented and is summarised in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime time horizon of 85 years.
Population	Adults and adolescents with APDS 12 years of age or older.
Comparators	The comparator was current clinical management. This comprised IRT, antimicrobial therapies, immunosuppressive therapies, HSCT, and tonsillectomies (representing surgical interventions). These were viewed to be representative of the treatments to manage the complex manifestations experienced by patients with APDS. Some of these treatments could also be incurred in the leniolisib arm.
Model description	A health state transition model was used with a total of 23 mutually exclusive health states. In the current clinical management arm, patients entered the model in the "alive not on leniolisib treatment" health state and could transition to the death state. In the leniolisib arm, patients entered the model in the "alive on leniolisib treatment" health state. Upon discontinuation of leniolisib, patients transitioned to one of 20 tunnel states each representing the specific year of discontinuation (from year 1 to year 20 plus). These tunnel states could account for the varying post-discontinuation risks over time for manifestations and associated management treatment use. Patients in the leniolisib arm could transition to the death state from any health state. For patients alive in either treatment arm, manifestation prevalence and associated treatment use for the management of manifestations were estimated using a partitioned approach.
Clinical data	In the current clinical management arm, data for overall survival, manifestation rates, and associated management treatment use were primarily from the cohort of individuals with APDS in the ESID registry. Limited inputs were from Study 2201 Part II. In the leniolisib arm, data on the impact of leniolisib on overall survival, discontinuation rates, manifestation rates, and associated management treatment use were sourced from Study 2201 Part II, Study 2201E1, the Early Access Programme (EAP), and clinical expert opinion.
Extrapolation	In the current clinical management arm, overall survival data from the ESID registry were extrapolated using an exponential distribution. Manifestation rates for lymphoproliferations, cytopenia, gastrointestinal manifestations, malignancies, bronchiectasis-associated airway disease, and advanced lung disease were derived directly from the ESID registry. The proportion of patients with infections was based on the cumulative incidence in the ESID registry, while the annual number of infections (3.476) was the annualised rate in the placebo arm of Study 2201 Part II. Rates of hearing loss were from the medical history of Study 2201 Part II. For treatment use rates associated with managing patients with manifestations, each episode of acute infection was assumed to incur antimicrobial use with prophylactic antimicrobial treatment based on the cumulative infection rate from the ESID registry. Rates of use for other treatments (IRT, immunosuppressive therapies, HSCT and tonsillectomies) were derived directly from the ESID registry. These treatment rates were not linked to specific manifestation rates, as each treatment may be used to address multiple manifestations. In the leniolisib arm, overall survival was assumed as that of the general population with a relative risk applied from Study 2201E1 and the EAP.

	Improvements in manifestations were captured through reduced incidence, resolution of prevalent manifestations, or reductions in severity based on Study 2201 Part II, Study 2201E1, EAP and clinical expert opinion. Where a proportion of patients did not experience resolution or reduced severity, no change was applied relative to the current clinical management arm. For lymphoproliferation, cytopenia, gastrointestinal manifestations, and advanced lung disease, no further incidence was applied. Incidence reductions were applied using hazard ratios for hearing loss (0.33), bronchiectasis-associated airway disease (0.28), and malignancies (0.41). Reductions in severity were applied for gastrointestinal manifestations (78%), bronchiectasis-associated airway disease (33%), and advanced lung disease (100%). Resolution of prevalent manifestations was modelled in lymphoproliferation (96%), cytopenia (78%), gastrointestinal manifestations (36%), and bronchiectasis-associated airway disease (10%). Annualised infection rates fell from year 1 to year 4 onwards. Treatment use rates associated with managing patients with manifestations were reduced to reflect these improvements. Antimicrobial use fell in line with lower infection rates. IRT use fell based on hazard ratios derived from Study 2201E1. Use of immunosuppressive therapies and tonsillectomy were reduced based on clinical expert opinion. HSCT was assumed to occur only following leniolisib discontinuation. As no treatment waning was assumed in the model, the impact of leniolisib on manifestations and associated treatment use was constant over time. An annual leniolisib discontinuation rate of 2.55% was applied derived from Study 2201E1 and the EAP. Following discontinuation, patients were assumed to revert to the manifestation risk profile prior to initiating leniolisib treatment. For patients that discontinue leniolisib, mortality was assumed to be that of the current clinical management arm.
Quality of life	Patients in the model were assigned an age-adjusted baseline APDS baseline utility, which was assumed to be that of the general population. As patients experienced various manifestations and received associated management treatments, their impact was applied to the baseline utility using disutilities or utility multipliers. These were sourced from published literature and clinical expert opinion. The combined impact of multiple manifestations and treatments was modelled using an additive approach. For patients receiving leniolisib who experienced reduced severity in certain manifestations, the corresponding utility decrements were reduced.
Costs and resource use	Costs included leniolisib acquisition, manifestations and associated management treatment use, and monitoring. For patients receiving leniolisib who experienced reduced severity in certain manifestations, the corresponding resource costs were reduced.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness results. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

5.2. Results

The economic modelling suggested that leniolisib would be associated with increased costs compared to clinical management. However, the modelling also indicated that leniolisib would generate positive health gains, estimated at 8.08 quality adjusted life years in the base case.

SMC is unable to publish the full economics results as incremental costs and incremental cost-effectiveness ratios have been classed as commercial in confidence by the submitting company.

5.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 5.3

Table 5.3: Sensitivity analysis results

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			CIC	8.08	CIC
1a	Discount rate (costs and benefits)	3.5%	0%	CIC	18.58	CIC
1b			6%	CIC	5.30	CIC
2	Time horizon	85 years	30 years	CIC	6.22	CIC
3a	Post-discontinuation manifestation risks and treatment use	Return to starting age risks at time of leniolisib initiation	Return to risks from age 0	CIC	8.11	CIC
3b			Age-specific current clinical management risks	CIC	8.24	CIC
3c			Catch-up to current clinical management prevalence	CIC	7.76	CIC
4	OS extrapolation – current clinical management	Exponential	Weibull	CIC	8.12	CIC
5a	Reduction in utility decrements for reduced severity manifestations	GI: 50% Bronchiectasis: 100% Advanced lung disease: 100%	All 100%	CIC	8.72	CIC
5b			All 50%	CIC	7.88	CIC
5c			All 25%	CIC	7.47	CIC
6a	Reduction in resource use for reduced severity manifestations	50%	100%	CIC	8.08	CIC
6b			25%	CIC	8.08	CIC
7	APDS Baseline utility	General population	Baseline SF-36 from Study 2201 Part II	CIC	7.35	CIC

Abbreviations: GI = gastrointestinal; ICER = incremental cost-effectiveness ratio; Incr = incremental; OS = overall survival; QALYs = quality-adjusted life years. CIC = Commercial in confidence. Note: For scenario 3c, where patients receive leniolisib for 10+ years, their risk returns to the starting age risk.

*Other data were also assessed but remain confidential.**

5.4. Key strengths:

- The current clinical management comparator was appropriate.
- The company provided probabilistic sensitivity analysis, one-way deterministic sensitivity analysis, and scenario analyses to understand parameter uncertainty in the economic analysis.
- The sources used to value medicine and resource costs were appropriate.

5.5. Key uncertainties:

- The economic analysis assumed no treatment waning for leniolisib. The submitting company highlighted that this was not expected, as there is no mechanism for patients with APDS to develop resistance to leniolisib and no evidence of treatment waning was observed in the leniolisib clinical studies. However, without longer-term data there is uncertainty in whether the treatment effect would be sustained. No treatment waning scenario analysis was available.
- There was uncertainty in how manifestations and associated management treatments would be affected following discontinuation of leniolisib. In the base case, based on the company's clinical expert preference, it was assumed that for patients who discontinued leniolisib, the annual risk of developing manifestations reverted to that of current clinical management at the time of leniolisib initiation. However, due to the evidence gap in this area, several alternative scenarios were explored (Scenario 3).
- There were uncertainties in the approach to utility values. Firstly, the submitting company used an additive approach to combine the utility decrements of manifestations. While NICE DSU TSD 12 notes there is no consensus on the most appropriate method, the multiplicative approach is recommended.[10] The submitting company noted both the additive and multiplicative approaches produced similar utility values for combinations of manifestations. However, it was observed that the multiplicative approach produced utility values that were slightly higher and therefore may have reduced incremental QALYs. No scenario analysis was available to evaluate this. In addition, various manifestation utility multipliers were the most sensitive parameters in one-way deterministic sensitivity analysis. Secondly, the baseline utility value was assumed to be equivalent to the general population. SF-36 data collected in Study 2201 and Study 2201E1 mapped to the EQ-5D-3L were available to generate an alternative baseline utility value. This was considered in scenario analysis, but a caveat is a potential double counting of manifestations given the inclusion criteria of these studies (Scenario 7). Finally, the model assumed reductions in the utility decrements for gastrointestinal manifestations, bronchiectasis-associated airway disease and advanced lung disease in patients with

reduced severity in these manifestations. Given uncertainty in the assumed reduction percentages, these were explored in scenario analysis (Scenario 5).

- There were uncertainties in the overall survival extrapolations. Overall survival in the leniolisib arm was assumed to be the general population adjusted by a relative risk. Further data to support the assumptions of this approach would be beneficial. In addition, the overall survival extrapolations were not directly linked to manifestation rates. Since a higher prevalence of manifestations would likely reduce survival, this omission may limit the accuracy of the survival modelling. However, incorporating this relationship would add complexity to the overall survival modelling.
- There was uncertainty in whether the one-way deterministic sensitivity analysis was sufficient to explore parameters affecting incidence reduction, resolution, and severity reduction for manifestations in the leniolisib arm. While these parameters were not identified as sensitive, multiple assumptions were used in their derivation, such as the use of Delphi panel thresholds to derive resolution percentages for lymphoproliferation and cytopenia. Furthermore, as lymphoproliferation, cytopenia, gastrointestinal manifestations, and advanced lung disease had zero incidence hazard ratios they were excluded from the analysis. It is noted that low counts of transient lymphoproliferation, cytopenia, as well as a gastrointestinal event in a patient with a baseline condition, were observed in Study 2201E1 and the EAP. The exclusion of zero incidence hazard ratios from one-way deterministic sensitivity analysis limited exploration of this uncertainty.
- There was uncertainty in the resource use reduction for patients experiencing less severe manifestations. The base case assumed a 50% reduction in the costs associated with less severe manifestations, based on company clinical expert opinion. However, given the percentage reduction was assumption based, scenario analysis considered alternatives (Scenario 6).

6. Costs to NHS and Personal Social Services

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

There are no relevant guidelines.

8. Additional information

8.1. Product availability date

April 2025

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Leniolisib	70mg orally twice daily	446,457

Costs from dm +d database on 27 October 2025. Costs do not take any patient access schemes into consideration.

References

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3. Busch K, Memmott HL, McLaughlin HM, et al. Genetic etiologies and outcomes in malignancy and mortality in activated phosphoinositide 3-Kinase delta syndrome: a systematic review. Adv Ther 2025; 42: 752–771.
4. US Food and Drug Administration (FDA). Leniolisib multi-discipline review, application number 217759Orig1s000. www.fda.gov.
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10. Ara R, Wailoo A. NICE DSU Technical Support Document 12: The Use of Health State Utility Values in Decision Models. London: National Institute for Health and Care Excellence (NICE); July 2011.

This assessment is based on data submitted by the applicant company up to and including 17 October 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and

advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.