Highly Specialised Technology

Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over [ID6130]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over [ID6130]

Contents:

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NICE National Institute for Health and Care Excellence

Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over [ID6130]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **12th December 2024**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pharming Technologies N.V.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Executive summary Pharming appreciates the opportunity to respond to the Draft Guidance prepared by the National Institute for Health and Care Excellence (NICE) for the evaluation of leniolisib for treating activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over. In response to the initial decision not to recommend leniolisib in this indication, Pharming are eager to address key concerns and resolve remaining uncertainty associated with the submission, in order to secure access for patients in England who have overwhelmingly demonstrated their support for availability of the treatment. It is important to consider this response in the context of the unmet need faced by patients with APDS in UK clinical practice. Individuals with APDS experience severe and progressive multi-system manifestations associated with both immune dysregulation and immune deficiency. Patients face a risk of developing malignancy in early life and end-organ damage accumulates over time,[1-5] causing APDS to significantly shorten life, with one in four people not surviving beyond age 21.[6-9] While symptoms may vary across the population of people with APDS, data from the APDS cohort in the European Society for Immunodeficiencies (ESID) registry indicate that by age 10 over 90% of people have experienced a manifestation which significantly or severely impacts quality of life manifestation,[10] and recently presented data from the UK Primary Immunodeficiency (PID) registry indicate lifetime risk of malignancy and lung disease to be near 100%.[11] While some patients may be stable today, the available data indicate this is unlikely to be sustained long-term, highlighting the importance of ongoing and proactive management. Further details about the significant manifestations experienced by almost all patients with APDS are provided in comment #4 below. Experiencing multiple, heterogenous manifestations simultaneously leads to cumulative, extreme impacts on health-related quality of life (HRQoL), mental health and daily activities.[3, 12-14] Individuals with APDS describe feeling exhausted and drained, both mentally and physically. They have described constantly “fighting with permanent anxiety that [their] body could let [them] down at any moment”, their loss of hope with “no plans for the future”, and feeling anxious regarding the risk of developing lymphoma and “not making it far”. Living with APDS therefore has broad and substantial impacts on individuals leading to anxiety, depression, stress and loss of hope,[15-18] with individuals struggling to live normal lives including performing daily activities, working and/or participating in education.[5] Moreover, as acknowledged during the evaluation committee meeting, carers of people with APDS have also reported depression, anxiety and

anger, reduced working hours and a substantial impact of APDS on relationships with loved ones and wider family life.[14]

There are currently no licensed treatments available for APDS in the UK. Despite receiving multiple symptomatic treatments concurrently, individuals with APDS continue to experience disease progression and life-threatening manifestations such as lymphoma (55% probability by age 46), resulting in a substantially reduced life expectancy compared to people without APDS.[1, 2, 5, 8, 19] Additionally, current treatments are often intensive and invasive in nature, requiring regular hospital stays,[2, 6, 14, 17-22] but are required to be taken long-term,[5, 23-25] and are associated with frequent and/or severe side effects.[2, 22, 26-28]

Leniolisib is the first and only targeted disease-modifying therapy for individuals with APDS, selectively inhibiting p110δ in the hyperactive PI3Kδ enzyme complex.[29] By normalising immune cell development, leniolisib ameliorates the immune dysregulation and immune deficiency observed, and provides patient-relevant benefits such as preventing the progression of manifestations, sparing or halting the use of symptomatic treatments and potentially preventing irreversible end-organ damage,[25, 30-34] all of which is expected to substantially reduce mortality, improve HRQoL and allow a full education and working life for the majority of patients.[14] A patient noted that they "feel like [they] took a life pill; [they] could breathe better and had more energy, and [they] could just do more things".[3, 35-37]

The economic model has undergone conceptual, technical and clinical validation to ensure it comprehensively and accurately represents the known impact of APDS on HRQoL and the healthcare system, and the impact of leniolisib. However, Pharming acknowledges that there are still gaps in the evidence base for leniolisib, creating some uncertainty within the economic modelling. Within this response, Pharming seeks to summarise overall responses to key issues raised in the Draft Guidance, provide responses to specific points, clarify evidence gaps and provide additional analyses in order to assuredly demonstrate the benefit that leniolisib provides to patients and the healthcare system.

Therefore, this response provides:

- A suggestion to clarify the wording referring to the committee's position on the lack of waning of treatment effect (comment #1)
- Clinician input and additional analyses on the rate of return of manifestations and treatments after discontinuation of leniolisib (comment #2)
- Additional evidence and clinician input reinforcing the emotional and wider impacts of APDS for patients and the benefits of leniolisib treatment that were not captured in the economic model (comment #3)
- Additional evidence and analyses supporting the criteria for use of a 1.5% annual discount rate for health benefits and costs (comment #4)

	• Explanation of the difference between the probabilistic and deterministic cost-effectiveness estimates (comment #5) Alongside this response, Pharming has provided an updated company base case and a revised simple patient access scheme (PAS) (further described in Appendix B and Appendix C), which includes the following inputs and assumptions: • Annual discount rates of 1.5% for both costs and health benefits (a scenario analysis uses annual discount rates of 3.5% for costs and health benefits, per the committee's preference in the draft guidance) • Sustained leniolisib benefit while on treatment (no change from the company submission base case) • Discontinuation rate of 2.7% per year based on continued follow-up in Study 2201E1 (May 2024 data cut), and the leniolisib Early Access Programme (EAP; 28 Nov 2024 data cut) • The treatment-specific utility gain with leniolisib treatment has been removed in line with the committee's preferred assumptions • The baseline utility is now sourced from general population values • The probabilistic analysis assumes a standard error of 10% around the mean values of model inputs without available values for uncertainty, in line with the committee's preferred assumptions • Addition of tunnel states in order to explore post-discontinuation risk assumptions. • New analyses of follow-up and mortality data for current clinical management and leniolisib • Revised hazard ratios (HRs) for the incidence of lymphoproliferation and malignancy The full results of the updated base case, and all relevant scenario analyses, are presented in Appendix B.
1	**Lifelong treatment effect assumed** As noted in Section 3.17 of the Draft Guidance, the committee's preferred assumption with regards to long-term treatment effect was that waning of the treatment effect of leniolisib was not expected. This was supported by the clinical experts, who explained that there is no mechanism for people to develop resistance to leniolisib, and that they could not see how treatment effect waning could occur since antibodies to leniolisib are not produced. No evidence of treatment waning has been observed in the leniolisib clinical trials, with up to six years of data from Study 2201E1 available.[32] Clinicians also agreed that APDS is unlikely to progress once the phosphoinositide 3-kinase delta (PI3Kδ) pathway is normalised by leniolisib, as APDS is not caused by any other mechanism. As of December 2024, 20 patients with APDS have received >4 years of leniolisib therapy, and amongst this group there have been no discontinuations. This indicates no long-term need for rescue medications or alternate therapies due to a treatment waning effect.

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2	**Treatment discontinuation rate** As noted in Section 3.11 of the Draft Guidance, the committee discussed the rate of discontinuation of leniolisib treatment modelled in the company's cost-effectiveness analysis during the evaluation committee meeting. The committee agreed with the company to use a discontinuation rate based on discontinuations observed in clinical and real-world use of leniolisib. Since the company submission, patients have continued to stay on therapy with a median (interquartile range [IQR]) of 1.8 (0.79 to 3.48) years of therapy across Study 2201 and the EAP as of Nov 2024, and 3.7 (3.2 to 4.6) for people who first received leniolisib in Study 2201. With 7 discontinuations in 291.9 patient-years of treatment in the EAP and Study 2201, the discontinuation rate has fallen to 2.7%. **Manifestation and treatment recurrence rates** As noted in Section 3.11 of the Draft Guidance, the committee also discussed the modelled rates of manifestations and treatment use, following leniolisib discontinuation. The company submission model used a three-stage model ("alive on leniolisib", "alive, not on leniolisib" and "dead") to estimate outcomes on leniolisib treatment. Patients who discontinued leniolisib treatment during each model cycle accumulated in the discontinuation state ("alive, not on leniolisib") over the course of the model time horizon. In the discontinuation state, the model applied the average annual incidence rate of manifestations and treatment for current clinical management, which was a simplifying assumption to manage the various risks for people who had discontinued leniolisib after 1 year, or 20 years, but were now in the same health state. The committee requested exploration of alternative scenarios for the returning risk of manifestations and treatment. In the revised model submitted as part of this response, Pharming has added tunnel states in order to separately model post-discontinuation events for patients discontinuing in the first 20 years. These tunnel states clearly show the different discontinuation cohorts per cycle, and can be found in Sheet "Leniolisib model engine" of the model supplied as part of this response. The below section describes exploration of post-discontinuation risk. **Scenario analyses exploring manifestation and treatment recurrence rates** As few people have discontinued leniolisib to date, there are limited data to inform estimates of post-discontinuation risk of manifestation recurrence and treatment use. To inform the clinical plausibility of various scenarios, Pharming conducted an Expert Gathering Exercise, gaining insights from six clinical experts in APDS from the UK to obtain their opinion and expectation of the potential return of manifestations and need for treatment for people who discontinue leniolisib after 1, 5, or 10+ years of therapy (Appendix A).

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	Upon leniolisib discontinuation, the clinical experts found it most clinically plausible for all manifestations risks to return to the risk before starting leniolisib treatment, irrespective of whether the patient had the manifestations before initiating leniolisib treatment. In general, the experts agreed that it was unlikely for manifestation and treatment prevalence to revert immediately upon discontinuation to the same levels as for people who had never been treated with leniolisib. Experts highlighted that for irreversible organ damage, such as advanced lung disease and hearing loss, leniolisib is expected to stabilise the condition. As a result, patients on treatment are more likely to maintain better overall health compared to untreated individuals of a similar age, and so disease progression post-discontinuation of leniolisib would start from a better state of health. The revised model includes an updated base case and scenario analyses for post-discontinuation risk, presented in Appendix B and Appendix C. **Participants in the Expert Gathering Exercise were also asked about other scenarios of post-discontinuation risk mentioned in the Draft Guidance:** ***(1) Reversion to annual incidence of each manifestation from birth*** Across all respondents, this was not seen to be the most likely scenario post-discontinuation. Some experts thought it could be related to how long patients had been on treatment, noting that the longer patients stay on therapy, the less likely these manifestations are to return, such as lymphoproliferation, autoimmune cytopenias, bronchiectasis-associated airways disease, advanced lung disease, malignancies and hearing loss. One respondent felt that a return to incidence rates from age 0 was most plausible for long-term manifestations (bronchiectasis, advanced lung disease, and malignancy) for people who had been on leniolisib for 5 to 10 years or more prior to discontinuation. ***(2) Reduced hazards reflecting lower risks in older people*** Four out of six clinical experts agreed that the risk of developing infections, gastrointestinal manifestations, and autoimmune cytopenias increases with age. Five out of six experts believed that the risk of lymphoproliferation also rises with age. All physicians unanimously agreed that the likelihood of developing bronchiectasis-associated airway disease, advanced lung disease, and malignancy increases with age. For this reason, this scenario was considered not plausible and therefore not considered in the updated base case. ***(3) Adjustment of hazards for duration of treatment*** In general, responses indicate that the most plausible long-term effect is that leniolisib stops manifestation development, and patients will again be subject to risk after discontinuing. However, one expert felt that risk may return to that of a younger patient (if not a newborn) after 5-10 or more years of treatment. When asked about the likelihood of people discontinuing after long-term (10+) treatment with leniolisib and eventually returning to the lifetime risk of current clinical management, 5/6 experts felt it was not plausible to return to lifetime risk for lymphoproliferation and malignancy, while the majority (at least 4/6) felt that it was either not plausible or somewhat

plausible to return to current clinical management lifetime risk for infections, gastrointestinal manifestations, autoimmune cytopenias, bronchiectasis, and advanced lung disease. Similarly, four of five respondents felt it is very plausible for people who discontinue leniolisib after 10+ years to subsequently have a lower mortality risk than people of the same age on current clinical management, versus 0/5 respondents indicating it would be very plausible for subsequently lower mortality risk when discontinuing after 1 year of leniolisib.

Immediate return to current clinical management rates of manifestations and treatment use

Given that changes to the constitution of the immune system may occur over a period of several years, as confirmed by the clinical experts during the meeting,[38, 39] it is clinically implausible that manifestations and treatment use would return to current clinical management rates immediately upon discontinuation of leniolisib treatment. For example, it was acknowledged by the clinical experts during the evaluation committee meeting that manifestation recurrence would be expected to occur over a period of months or years, and that immune dysregulation manifestations such as lung disease and lymphoma would take time to recur. Furthermore, the majority of the clinical experts considered it not to be plausible to return to the standard of care lifetime risk for lymphoproliferation, infections, gastrointestinal manifestations, bronchiectasis-associated airways disease and malignancy after long-term treatment use (10+ years).

In the Expert Gathering Exercise, no expert responded that the risk in the year post-discontinuation would be plausibly higher than that of someone on current clinical management (Appendix A). Even for people who were treated with leniolisib for 10 or more years, only one respondent felt it was plausible that people would eventually return to current clinical management risk. Finally, all respondents felt that mortality benefits are somewhat plausible with just one year of leniolisib treatment, while mortality equal to current clinical management after one year of treatment would be either very plausible (2/6) or somewhat plausible (4/6).

Given the unlikelihood of treatment benefits being immediately unwound, an immediate return to current clinical management rates for all patients has not been modelled. A scenario analysis does consider the possibility of event probabilities post-discontinuation which are higher than current clinical management, in order to return people with <10 years of leniolisib therapy to current clinical management cumulative incidence curves; this is described in Appendix B with results presented as scenario 2b.

Conclusion

In the updated model submitted as part of this response, Pharming has added tunnel states in order to separately model post-discontinuation events for patients discontinuing leniolisib in the first 20 years; these tunnel states clearly show the different discontinuation cohorts per cycle.

As few people have discontinued leniolisib to date, there are limited data to inform estimates of post-discontinuation risk. Therefore, Pharming has conducted scenario analyses which explore clinically plausible possibilities for post-discontinuation risks, informed by expert opinion. In these scenario analyses, the ICER improved or did not substantially increase compared with the

	updated base case. Therefore, having established the clinical plausibility of different post-discontinuation risks, Pharming considers that the impact of the associated uncertainty is small.
3	**Removal of additional utility gain of 0.1** Pharming has removed the 0.1 utility gain from the revised economic model submitted as part of this response, as per the committee's preferred assumptions. However, this underestimates the QALYs accrued in the leniolisib arm by excluding benefits of leniolisib that are not explicitly modelled in the economic analysis, and we ask the committee to consider these in their decision-making. More information regarding these benefits is provided in comment #4 below. A scenario analysis is presented with the 0.1 utility gain in Appendix B.
4	**Wider, uncaptured benefits of leniolisib treatment** As a hereditary disease affecting people from a young age, with both physical and mental health symptoms, APDS has a wide-reaching impact on people living with the condition and their families. APDS significantly affects the lives of those living with the condition beyond its impact on physical and mental health, as it affects individuals' educational progress, work and emotional well-being, as well as the overall quality of life of caregivers and families of those living with APDS. A treatment correcting the hyperactive signalling pathway at the core of APDS can be expected to also have wide-reaching impact, and leniolisib treatment is associated with improvements in a number of manifestations in APDS, resulting in improvements in patients' quality of life.[40] Leniolisib is expected to offer benefits in areas beyond those captured in the economic model, including manifestations not modelled such as fatigue, psychosocial impacts, hope and addressing inequality. Moreover, leniolisib is expected to provide improvements to carer quality of life and a decreased societal cost, also not captured in the economic analysis. However, due to the difficulty in using the EQ-5D to quantify these benefits and demonstrate that they not been considered in the model, in the updated base case, the 0.1 utility gain has been removed, but Pharming asks that the committee considers these uncaptured benefits in its decision-making. **Leniolisib treatment improves key manifestations in APDS, including fatigue, which were not included in the economic model** The Expert Gathering Exercise asked clinicians (experienced in treating people with APDS) to list manifestations which were not modelled where leniolisib is expected to have an impact. Manifestations not captured included short stature and potentially neurodevelopmental concerns in APDS2. A systematic review of the impact of short stature on HRQoL found that short stature impacts the HRQoL of children, with this impact persisting into adulthood, and the caregiving burden is also increased; changes in height were sometimes significantly associated with changes in HRQoL.[41] Additionally, individuals with a diagnosis of PID have demonstrated significant perceived memory impairment, moderate anxiety, and mild to moderate depression when compared to normative scores.[42] Fatigue and symptoms associated with SHORT syndrome, which is linked to APDS2, may also affect daily functioning. Arthritis has been reported

in some patients with APDS; a meta-analysis indicates that rheumatoid arthritis has a substantial impact on HRQoL (SF-36 physical component summary score: 34.1 [95% CI: 22.0–46.1] compared to 50.0 in the general population).[43] Pain, congestion and damage as a consequence of lymphadenopathy should be considered, particularly in relation to pulmonary, airway and gastrointestinal obstruction. Chronic sinusitis may lead to a loss of smell, while glomerulonephritis has also been observed, which has been reported to have a strong association with HRQoL in multivariable analysis (adjusted β [95% CI] for composite PROMIS score in children, -5.2 [-7.1 to -3.4]; for composite PROMIS score in adults, -6.1 [-7.4 to -4.9]).[44] Additionally, some patients have experienced transverse myelitis and neuropsychological issues may further complicate the condition; these issues can impair mobility, bowel function, sleep quality and HRQoL.[45] They expect leniolisib to have a positive impact on all of these, except for some uncertainty around the impact on the central nervous system and neurophysiological issues. However, emerging data are encouraging; a case series of 10 patients (six under 12 years old, four between ages 12 and 18) found statistically significant improvement in the emotional and school functioning scales of the PedsQL, with a trend towards improvement in the physical and social functioning scales.[46]

Fatigue is commonly reported by individuals with APDS, as well as in other primary immune deficiencies where it may be unrelated to disease activity.[47-49] In the Immunodeficiency UK (IDUK) survey, most respondents (n=10/13) noted experiencing an extreme or moderate amount of tiredness due to APDS.[14, 18] As such, individuals frequently report being tired after exercise but also after daily activities, such as decision-making at work and/or cooking meals.[14] However, the EQ-5D assessment does not capture the impact of fatigue on HRQoL in a number of rare diseases.[50]

*"**Tiredness** and chest infections are a major concern as well as the mental anxiety the condition causes"*

*"Tough, **exhausting**, damaging, poorly, sick, irritable from coughing and all the infections, painful"*

The IDUK survey highlights several other known benefits of leniolisib treatment that were not modelled in the company's economic analysis, including reduced fatigue. Available qualitative data from patients reporting on their leniolisib treatment experience revealed that one third of participants explicitly attributed improvements in fatigue/energy to leniolisib. Increased energy levels were associated with HRQoL improvements, and included increased physical activity (33.3%), improvements in work/school performance/attendance (13.9%) and travel ability (8.3%).[51]

Improvements in fatigue in patients with common variable immunodeficiency was reported to result in better quality of life and patient-reported health outcomes.[52] As these improvements were not modelled in the economic analysis, with fatigue in particular being unrelated to disease activity and not captured by EQ-5D,[50] the significant benefit of leniolisib was not fully captured.

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APDS is associated with emotional distress and a wider burden on patients; the impact of leniolisib on alleviating this burden may not be fully captured in the economic analysis

APDS affects multiple aspects of patients' quality of life that are unlikely to have been captured in an EQ-5D quality of life assessment. In the IDUK survey of individuals with APDS, many respondents expressed that their disease affected their family life (n=8/14) and ability to socialise (n=5/14). When asked about the impact of APDS on quality of life, only four out of 13 respondents reported being satisfied with their quality of life.

Individuals with APDS often report experiencing emotional distress related to their condition. A study from the Netherlands found that people with inborn errors of immunity (IEIs) like APDS have significantly higher levels of mental health issues (e.g. distress and somatisation) compared to age-matched controls, largely due to fear of infections, social isolation, maladaptation, and concerns about the future.[53, 54] This evidence aligns with the results of the IDUK survey in which respondents described their emotional distress due to the burden of medical care, feelings of isolation, loneliness and frustration related to APDS. A prominent concern is the heightened risk of infection, with 11 out of 13 respondents reporting an extreme amount of concern over this issue, particularly in light of vulnerabilities such as COVID-19. In addition, individuals often experience constant anxiety about the unpredictability and progression of APDS, which is often accompanied by a sense of hopelessness for the future therefore,[17, 18, 55] In the IDUK survey, 11 respondents also reported an extreme or moderate extent of worry about future health, further adding to the emotional burden of living with APDS.

The testimonies of those affected capture the emotional toll of APDS.[14]

> *"Not easy, always on the edge, always following to the dot the doctors/CNS instructions/admissions a lot in hospital and **missing out on his childhood**/not being able to do a lot due to extreme precautions of the condition/not being able to see a lot of the family"*

> *"**Extremely worried** as he's unable to fight a cold without being hospitalise and IV antibiotics"*

> *"[my condition] makes me feel so down and depressed, **isolated**"*

> *"**Uncertainty** having a condition no one understands"*

Clinical evidence in the company submission demonstrates that leniolisib provides long-term and clinically meaningful benefits to people with APDS across a wide range of endpoints. By alleviating manifestations and preventing infections and further organ damage, leniolisib is anticipated to reduce the emotional burden and social isolation associated with APDS. Additionally, leniolisib treatment led to fewer hospital admissions, as data from the EAP showed a >50% reduction in hospitalisation rates for individuals after initiating leniolisib treatment.[56] This is likely to reduce the emotional and wider burden of APDS and improve patients' quality of life. However, these benefits are unlikely to be fully captured in the economic analysis, as hope for the

future is not captured by the EQ-5D,[57] nor is hope (or fear) valued in the time trade-off methods used to generate EQ-5D value sets.[58]

*"I feel like I took a life pill. I could **breathe better** and had **more energy**, and I could just do more things"*

APDS also impacts education and work; leniolisib has been shown to alleviate these impacts of APDS but this was not captured in the economic analysis

APDS has a pronounced impact on education and individuals with APDS typically have lower educational achievements than others, which cannot be accounted for by chronic illness effects alone.[5] The majority of respondents in the IDUK survey reported an impact on the ability to attend school or participate in educational activities (n=10) and reported significant days off (n=12), ranging from several weeks per term to as long as 1–4 years. Moreover, the burden of disease and increased isolation can also have a negative impact on adolescents' social life and development. As the EQ-5D scale lacks a psycho-social dimension, these impacts would not have been captured in the economic model.[59] Mothers of children with APDS mentioned how the challenges associated with the disease contribute to their children falling behind academically and socially, likely impacting their life in the long-term, which cross-sectional quality-of-life assessments are unlikely to capture.[14]

*"Recurrent infections, stunted growth, hearing issues **impacting learning in school**, ability to do physical sport, coordination issues"*

*"Ear and lymph glands problems. **Behind in schoolwork** and development **both socially and academically**"*

Available qualitative data from patients reporting on their leniolisib treatment experience saw improvements in work/school performance/attendance (13.9% of patients).[51] Additionally, leniolisib treatment reduced work absenteeism as demonstrated by the Work Productivity and Activity Impairment (WPAI) results of Study 2201E1, where the mean number of hours worked per week increased from 14.3 hours at baseline to 29.5 hours at Week 208.[32] Based on the UK median hourly earnings of £18.64 reported by the Office for National Statistics,[60] the additional 11.7 hours worked would result in an estimated increase of £218 in earnings per week, and a proportionate decrease in societal costs accrued. These benefits of leniolisib treatment were not captured in the economic analysis.

Leniolisib treatment is likely to reduce the burden on carers and have wider societal benefits

The effects of APDS extend beyond patients to significantly impact carers, affecting their ability to maintain employment and resulting in a loss of income. Four out of seven respondents indicated how APDS hinders carers' employment capabilities and financial strains experienced by families.[14]

"2-3 physio sessions a day, medicine administrations, weekly subcutaneous infusions, frequent soiling as on antibiotics regularly"

"delayed development so not potty trained and can't wash himself"

*"I am **unable to work** due to [the patient's] condition as she is constantly getting infections and needs IV medication at least 2/3 monthly"*

*"Significantly, my mother had to **give up work**, family holidays had to be cancelled, hobbies for my siblings had to be cancelled, time my parents spent with my siblings was compromised as they were always with me"*

Caregivers expressed the emotional relief at the potential for an effective therapy.

"Just having the chance to try a medication for a condition of this nature gives us just that little bit of hope that she will one day be healthier than what she is today"

Treatment with leniolisib is expected to reduce these burdens on caregivers, and thereby decrease the loss of income and productivity. All physicians agreed that leniolisib treatment would have a significant positive impact on the quality of life of caregivers, as carers often experience anxiety and disruptions to their work and daily lives, including staying home due to their child's illness. With new treatment options, caregivers now have more control, potentially avoiding HSCT or gaining time to prepare for it, including finding a suitable donor. Leniolisib can also offer an improved safety profile compared to options like prolonged steroid use or sirolimus, reducing hospital visits and monitoring requirements. Parents are seeing positive outcomes, such as fewer infections and increased energy in their children. Overall, these treatment responses can greatly improve the quality of life for caregivers, especially if the patient requires less care and is able to return to work. The reduction in hospitalisations required after initiating leniolisib treatment, as reported in the EAP,[56] is also likely to significantly reduce the societal costs associated with APDS.

Another uncaptured benefit is how the availability of leniolisib might address the inequality associated with haematopoietic stem cell transplantation (HSCT). Patients from ethnic minority backgrounds report difficulty in finding a suitably matched unrelated donor for HSCT. According to information from the international charity DKMS, patients from black, Asian, or other minority backgrounds have only a 20% chance of finding the best possible blood stem cell match from an unrelated donor in the UK, compared with a 69% chance for individuals of northern European backgrounds.[61] While leniolisib is anticipated to be positioned as a treatment option for all adults and adolescents with APDS, it also offers a crucial alternative for those unable to undergo HSCT, addressing the inequality. The mother of a child affected by APDS emphasised this point. Furthermore, some patients refuse to undergo HSCT due to having witnessed their family members endure suboptimal outcomes for HSCT for management of their own APDS. As such,

	these patient especially lack hope and can only envisage progressive clinical decline.[14] *"[the child] is unable to have a bone marrow transplant due to her ethnicity. I feel like if this medication was used for patients in the UK who are unable to get a transplant they would have more of a chance of living a more fulfilled quality of life"* **Hope due to treatment** Finally, in Section 3.12 of the Draft Guidance, it is mentioned that "many new and existing treatments provide increased hope to people with APDS". However, Pharming is not aware of which treatments are being referred to, nor any evidence to support this statement for any treatment options apart from leniolisib. The hope offered to patients by leniolisib treatment is likely to lead to improvement in HRQoL, which is not captured in the economic model. **Conclusion** Overall, APDS causes significant emotional distress, fatigue, and long-term social and educational deficits, which were not explicitly modelled and would not be fully captured in the economic model unless treatment-specific utilities are considered. Leniolisib is expected to offer substantial benefits to patient quality of life in areas beyond those captured in the economic model, including physical, mental health and emotional improvements and broader social impacts. Beyond the direct benefits to patients, leniolisib treatment is expected to significantly reduce the impact of APDS on caregivers and society overall. Based on the heterogeneity of APDS impacts, Pharming acknowledges that it is challenging to accurately quantify the uncaptured benefit of leniolisib treatment. Therefore, the 0.1 utility gain for patients receiving leniolisib in the economic model has been removed in the updated base case. There are hence substantial benefits associated with leniolisib treatment for patients, caregivers and the wider society, which are not reflected in the QALY gain estimated in the economic model. Therefore, Pharming ask that the committee consider the potential size of the uncaptured benefit of leniolisib treatment to patients, carers and wider society in its decision making.
5	**1.5% non-reference case discount rate** As noted in Section 3.13 of the Draft Guidance, the committee accepted that criterion 3 for use of a 1.5% annual discount rate for health benefits and costs (sustained benefits likely over a very long period) has been met. Therefore, this response focuses on criteria 1 and 2. **Criterion 1: The technology is for people who would otherwise die or have a very severely impaired life** There is sufficient evidence to support that quality and length of life is significantly reduced and impaired amongst nearly all individuals with this ultra-rare condition, as detailed below, and criterion 1 is thus met. NICE previously acknowledged this when this evaluation met HST criterion 3 ("the very rare condition significantly shortens life or severely impairs its quality"), for which

almost all patients must be impacted. In its assessment of the routing of this evaluation, the NICE Topic Selection and Oversight Panel (TSOP) acknowledged that "although there is some heterogeneity with the condition, the TSOP panel agreed that quality of life is severely impacted for the majority of people". In addition, recently presented data from the UKPID registry illustrate lifetime risk of malignancy or lung disease to be at or near 100%, with 43% of people with lung disease having a forced expiratory volume in one second (FEV1) <70% predicted.[11] While these estimates are based on data from approximately 60 patients, they are consistent with analyses of the ESID registry and literature which show the high prevalence of manifestations which severely impact quality of life and increase the risk of mortality.[10]

Patients with APDS have severe disease from early in life

It was noted in the Draft Guidance response that APDS presents as a heterogeneous disease. Whilst Pharming acknowledges this to be true, as familial testing can diagnose cases prior to symptom development in a minority of patients, APDS is diagnosed due to malignant lymphoma in 21% of cases, with half of malignancies occurring before the age of 20 in published literature[7] and in the UKPID registry.[11] Given the high incidence of lymphomas, near-universal lifetime prevalence of lung disease, and recurrent infections despite antibiotic prophylaxis and immunoglobulin replacement therapy (IRT) use,[1, 10, 19] it is likely that people with APDS will have experienced disease manifestations prior to diagnosis. This is supported by findings from a recent SLR that there is a gap of approximately 10 years between the average age of first symptom and average age of diagnosis (13.4 years old) for individuals with APDS.[62] The delay may be shorter in the UK, with a median age of APDS diagnosis of 9.17 years.[11]

Section 3.2 of the Draft Guidance states that "APDS can be an asymptomatic condition", however there has only been a single report in literature regarding one patient (out of a cohort of 53 with APDS) who was asymptomatic, and whose age was unspecified.[1] In addition, there are only three patients with APDS included in the ESID dataset with no reported symptoms, however, each of these patients has only the registration visit captured and no follow-up data, so this may reflect poor reporting.[37] Of relevance to the population addressed by this submission, adolescents and adults aged 12 years and older, a recent analysis of the ESID registry by Thalhammer et al., 2021 found that by the age of 10, >90% of patients with APDS had presented with at least one manifestation (March 2019 dataset).[63] In a recent systematic literature review, the mean age of first symptoms was 2 years (range 0.003 to 22 years).[62] Overall, only a small minority of patients diagnosed with APDS may not have experienced manifestations by the age of 12.

Even for patients who are diagnosed prior to onset of severe disease, it is clear that disease progression leads to significant reductions in the quality and length of life of all individuals with APDS

Published case studies and analyses indicate that APDS is associated with a significant shortening of life, with one in four people not surviving into early adulthood.[6-9]

- A literature review by Hanson and Bonnen, 2024 identified 256 published cases of APDS and provided evidence on survival. Figure 1 presents the survival analysis based on these

cases and indicates that APDS considerably shortens life, with a conditional survival rate of 68% for individuals with APDS aged 40 years[8]

- More recently, a survival analysis was conducted by Pharming, utilising a more recent data cut-off of the cohort in the Hanson and Bonnen, 2024 publication (January 2022 dataset).[64] Among the 351 included individuals with APDS, 41 (11.7%) deaths had occurred, and the estimated probability of survival dropped to 25% by 65 years of age.[64] This case series offers the most comprehensive and up-to-date mortality data currently available for individuals with APDS

These published case series assumed all people with APDS were observed from birth, and did not account for left truncation, which is likely to cause overestimation of survival for people with APDS, for several reasons:

- Survivor bias: Individuals who are included in the study have already survived up to the point of entry, which means those who died before this point are not represented. This can make the survival probabilities appear higher than they actually are.
- Underestimation of early events: events (such as deaths) that occur before the entry point are not observed, leading to an underestimation of the risk of early events. This skews the survival curve, particularly in the early time periods.
- Distorted survival estimates: the survival estimates may not accurately reflect the true survival distribution of the population, as the sample is biased towards those who have survived longer.

Expert opinion is that mortality in APDS is likely to be significantly under-reported,[11] and the above factors may explain the discrepancy between literature-based estimates of median survival greater than age 55, with:

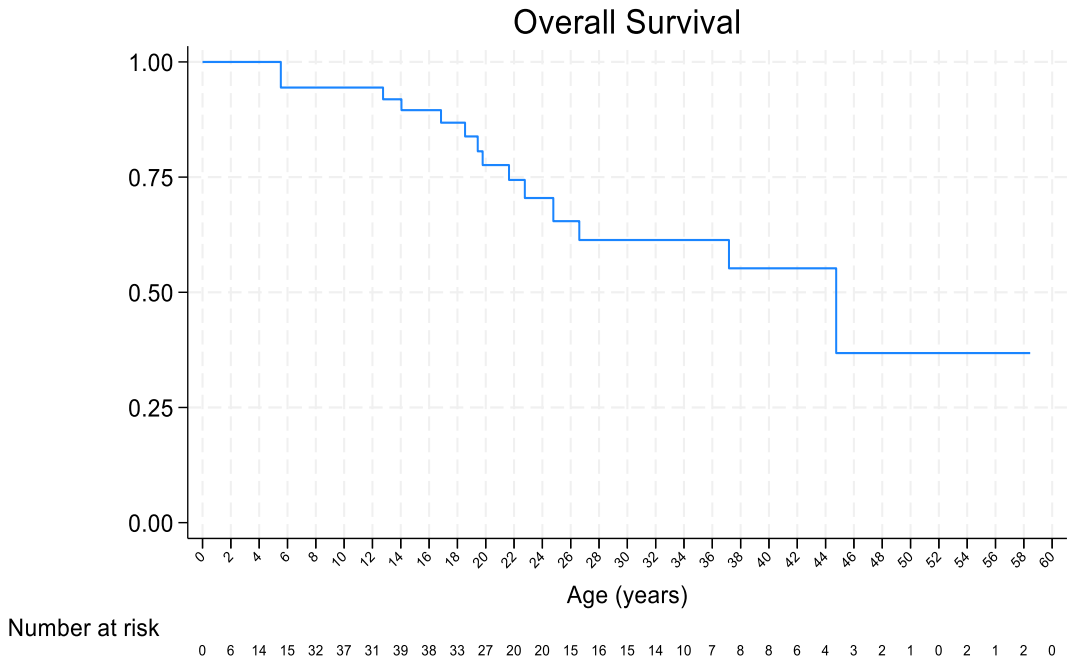
- A median age of death of 18.5 years (range 5-44 years) in the recent publication by Maccari et al.[3]
- Despite the use of family screening, only 6% of known patients in literature have reached age 40,[64] and only 13% of alive patients in the UK have reached age 40

The UK clinical immunology community acknowledges that the UKPID registry, the largest contributor of UK data to the ESID registry, underreports the mortality rate of APDS as multiple people with APDS in the UK are known to have deceased over the past 5 years who were not included in the registry by the time of their death.[65] Furthermore, people who develop lymphoma secondary to APDS will likely be managed for lymphoma without the underlying diagnosis being determined, unless other manifestations of APDS are recognised to have preceded the lymphoma.[65]

To reduce some impact of left truncation, data from the ESID registry (data cut 26 Nov 2024) were analysed from the age of registration to either death or the last visit in the dataset.[10] This analysis included 158 people with APDS, with a mean (SD) age at entry of 15.7 (11.8) and a median follow-up of 4.70 (95% CI: 4.06 to 5.73) years. Figure 1 presents the results of Kaplan-

Meier analysis, where 13 deaths were reported. This analysis indicates 25% mortality by age 21, and median survival of 44 years.

Figure 1: Survival in the ESID registry



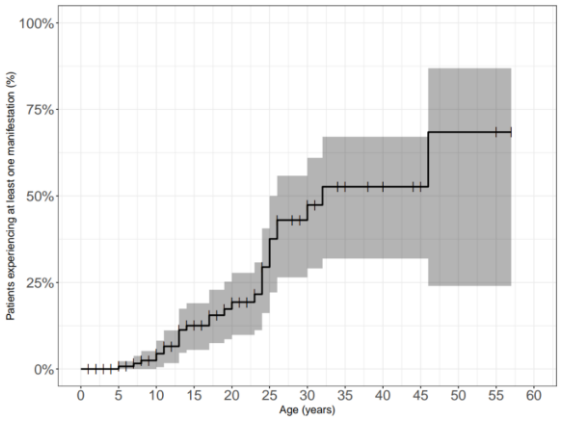
Abbreviations: ESID: European Society for Immunodeficiencies.
Source: Pharming Data on File, 2024.[10]

Across patient lifetimes, APDS is unlikely to have heterogeneous severity

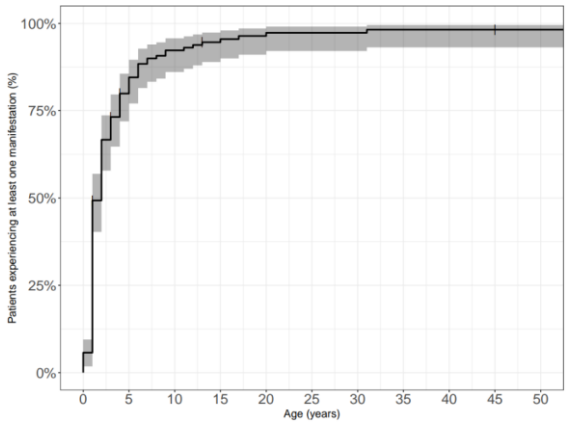
In the Expert Gathering Exercise, the majority of respondents believed that advanced lung disease and malignancies have a severe impact on quality of life, and infections, gastrointestinal manifestations, and hearing loss have a significant impact on quality of life. Figure 2 shows that by age 46, 63% of individuals with APDS had experienced at least one severe manifestation, while by age 10 over 90% had experienced a significant or severe manifestation, demonstrating that almost all patients with APDS experience severe or significant disease. As described previously, recently presented data from the UKPID registry indicate lifetime risk of malignancy and lung disease to be near 100%.[11]

Figure 2. a) Cumulative incidence of at least one severe manifestation and b) at least one severe or significant manifestation for individuals with APDS in the ESID registry cohort (November 2023 dataset)[a]

a)



b)



Footnote: [a]Individuals with missing data were not removed. Hearing loss was excluded because the age of onset is not captured in the ESID dataset.
Abbreviations: APDS: activated PI3Kδ syndrome; ESID: European Society for Immunodeficiencies.
Source: Pharming Data on File, 2023.[37]

Together, these expert responses and ESID data explain why only 31% of respondents to the IDUK survey reported satisfaction with their quality of life. Respondents reported that manifestations of APDS with an extreme impact included respiratory infections, cough, bronchiectasis and enlarged lymph nodes, with Table 1 (Appendix A) showing the extent of the impact of different aspects of APDS on quality of life. This evidence suggests that infections and lymphadenopathy, which are near-universal in APDS, have a substantial impact on the majority of people with APDS, further demonstrating the impact that APDS has on all patients.

Finally, in the draft guidance, the committee stated that increased testing may lead to increased heterogeneity. However, this conclusion overlooks the likelihood that testing will most likely occur in cohorts with some form of morbidity. As a result, any shift in heterogeneity is likely to skew toward the severe end of the disease spectrum. This point is exemplified by the fact that APDS has not been included in the Generation Study being conducted by Genomics England but rather it's the likes of the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) European Bronchiectasis Registry that are planning to identify underlying IEIs like APDS for patients with already advanced lung disease. Further, in terms of standard of care, the specialties that are would be referrers to clinical immunology will rarely refer asymptomatic patients to immunology services so again this will enrich the diagnosed population to the more severe end of the heterogeneity spectrum.[66]

This critical nuance, particularly in cohorts such as those with bronchiectasis or lymphoma, should be carefully considered in the committee's evaluation.

	Criterion 2: It is likely to restore them to full or near-full health Leniolisib, as a treatment targeted to the cause of APDS, has the potential to restore patients with APDS to full or near-full health. In Section 3.10 of the Draft Guidance, clinical experts noted that improved immune cell function is likely to be biologically sustained over time, which was acknowledged by the committee. In the Expert Gathering Exercise, the vast majority of clinical experts agreed that the short-term immune reconstitution seen with leniolisib could translate into long-term immune competence. (One expert chose not to agree or disagree with this statement, waiting for long-term data.) It is noteworthy that, in HST7, the committee was reassured by clinical experts that short-term immune reconstitution, leading to long-term immune competence, was expected to enable patients with ADA-SCID (also a combined immunodeficiency) to achieve normal or near-normal health.[67] Based on feedback from the experts, this evidence suggests a similar perspective should be applied for leniolisib in APDS, due to similarities between the two cases. Two cases have highlighted the transformative potential of leniolisib for individuals with APDS experiencing severe disease, restoring full health.[68, 69] One case involved a patient with significant lung damage, unsuitable for lung transplant or HSCT, not responsive to sirolimus, with 88% oxygen saturation on room air and poor quality of life.[68] Following treatment with leniolisib, oxygen saturation returned to 98% on room air, and the person returned to university and work with improved exercise tolerance. A second case concerned an individual who had undergone an unsuccessful HSCT and experienced severe gastrointestinal symptoms, and septic shock.[69] Following leniolisib, the patient experienced significant improvement in quality of life and was able to work; while the patient continued to have a stable, moderate ventilatory dysfunction, there were no respiratory symptoms or infections and antibiotic prophylaxis could be discontinued. In the Expert Gathering Exercise, respondents did not foresee any impacts of APDS and its manifestations to significantly limit activities of daily living for people treated with leniolisib. The majority of clinicians found that advanced lung disease and malignancies have the most severe impact on quality of life, and ≥50% rated infections, gastrointestinal manifestations, autoimmune cytopenias, bronchiectasis-associated airways disease and hearing loss to have a significant impact on patient's quality of life. During Study 2201 and the EAP, there were no new reports of advanced lung disease. While two malignancies have occurred during leniolisib treatment (considered to be unrelated to treatment), there are no treatments that can prevent cancer and this rate is almost a 50% reduction from current clinical management. Reported improvements in gastrointestinal symptoms and cytopenias in the EAP survey, and reductions in infections observed during the Study 2201E1, also indicate a return to normal health. By allowing even the most severe patients to return to work or school, improving quality of life, minimising development of severe manifestations, the available evidence indicates patients are able to experience full or near-full health as a result of treatment with leniolisib. While some patients who start leniolisib later in the course of disease may have accumulated some

	irreversible organ damage, lack of further progression and resolution of reversible aspects of disease offers huge value to quality of life. **Conclusion** Overall, analyses of the APDS cohort in the ESID registry demonstrate that most patients with APDS experience manifestations from early in life. Even for patients who do not experience severe disease at diagnosis, disease progression leads to significant reductions in the quality and length of life of all individuals with APDS due to the development of severe manifestations such as advanced lung disease and malignancies. Real-world use of leniolisib treatment and clinical opinion indicate that leniolisib treatment is anticipated to alleviate the HRQoL impact of APDS manifestations, restoring the majority of patients to full or near-full health. Based on treatment initiation during adolescence and the benefits of leniolisib treatment being experienced over a patient's lifetime, Pharming considers it important to avoid diminishing future health gains associated with leniolisib treatment and considers that NICE's criteria for use of a 1.5% annual discount rate have been met. Therefore, accepting NICE's preference for equal discounting, the updated base case in Appendix B uses a 1.5% annual discount rate for health benefits and costs.
6	**Model uncertainty – probabilistic sensitivity analysis** **Standard error assumption** In the probabilistic base-case cost-effectiveness analysis included within the company submission, standard errors were assumed to take values equal to 10% of that of the means for model inputs that did not have empirical probability distributions. As noted in the company's response to the EAG clarifications stage of this evaluation, the value of 10% was assumed based on a review of prior NICE evaluations.[70] Varying the assumed size of the standard error from 10% to 20% had a small impact on cost-effectiveness estimates. The assumption of 10% was considered reasonable by the NICE committee. In recognition of the NICE committee's preferred assumption, the company's updated probabilistic base case cost-effectiveness estimates presented in Appendix B continue to assume a 10% standard error around parameter means. After alterations to the model structure to incorporate tunnel states, and subsequent error checking, the probabilistic and deterministic analyses provide similar results in the revised model.

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Consultation on the draft guidance document – deadline for comments 5pm on **12th December 2024**. Please submit via NICE Docs.

References

1. Coulter, TI; Chandra, A; Bacon, CM *et al.* Clinical Spectrum and Features of Activated Phosphoinositide 3-Kinase δ Syndrome: A Large Patient Cohort Study. Journal of Allergy and Clinical Immunology. 2017;139(2):597–606.
2. Coulter, TI; Cant, AJ. The Treatment of Activated PI3Kδ Syndrome. Frontiers in Immunology. 2018;9.
3. Maccari, ME; Wolkewitz, M; Schwab, C *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.
4. All About APDS. APDS Features. Available from: https://www.allaboutapds.eu/apds-features/. Last accessed: August 2022.
5. Pharming Data on File. Leniolisib Expert Perspective and Insight Consultancy to Inform UK Health Technology Assessment. 2024.
6. Elkaim, E; Neven, B; Bruneau, J *et al.* Clinical and Immunologic Phenotype Associated with Activated Phosphoinositide 3-Kinase δ Syndrome 2: A Cohort Study. Journal of Allergy and Clinical Immunology. 2016;138(1):210–218.
7. Jamee, M; Moniri, S; Zaki-Dizaji, M *et al.* Clinical, Immunological, and Genetic Features in Patients with Activated PI3Kδ Syndrome (APDS): A Systematic Review. Clinical Reviews in Allergy Immunology. 2019;59(3):323–333.
8. Hanson, J; Bonnen, PE. Systematic review of mortality and survival rates for APDS. Clin Exp Med. 2024;24(1):17.
9. Okano, T; Imai, K; Tsujita, Y *et al.* Hematopoietic Stem Cell Transplantation for Progressive Combined Immunodeficiency and Lymphoproliferation in Patients with Activated Phosphatidylinositol-3-OH Kinase δ Syndrome Type 1. Journal of Allergy and Clinical Immunology. 2019;143(1):266-275.
10. Pharming Data on File. Natural History of Clinical Manifestations in Activated Phosphoinositide 3-Kinase δ Syndrome (APDS): Time-to-Event Analyses using the European Society for Immunodeficiencies-APDS Registry. [Manuscript In Development]. 2024.
11. Shillitoe, B. Activated phosphoinositide 3-kinase syndrome outcomes in the UK: An update from the UKPID registry. 2024. British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN) Conference; 10th December 2024.
12. Tessarin, G; Rossi, S; Baronio, M *et al.* Activated Phosphoinositide 3-Kinase Delta Syndrome 1: Clinical and Immunological Data from an Italian Cohort of Patients. J Clin Med. 2020;9(10).
13. Ewertowska, M; Grześk, E; Urbańczyk, A *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 & Clinical Immunology. 2020;16(1):22.
14. Immunodeficiency UK. Impact of APDS survey on patients and their carers. 2024.
15. Rider, NL; Kutac, C; Hajjar, J *et al.* Health-Related Quality of Life in Adult Patients with Common Variable Immunodeficiency Disorders and Impact of Treatment. J Clin Immunol. 2017;37(5):461-475.
16. Jiang, F; Torgerson, TR; Ayars, AG. Health-related quality of life in patients with primary immunodeficiency disease. Allergy Asthma Clin Immunol. 2015;11:27.
17. Pharming Data on File. Qualitative Study of Burden of APDS Report. 2023.
18. Pharming Data on File. Time trade-off (TTO) study in activated phosphoinositide 3-kinase δ (PI3Kδ) syndrome (APDS) report. 2023.
19. Maccari, ME; Abolhassani, H; Aghamohammadi, A *et al.* Disease Evolution and Response to Rapamycin in Activated Phosphoinositide 3-Kinase δ Syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase δ Syndrome Registry. Frontiers in Immunology. 2018;9(543):1–8.
20. Lucas, CL; Kuehn, HS; Zhao, F *et al.* Dominant-Activating Germline Mutations in The Gene Encoding The PI(3)K Catalytic Subunit p110δ Resulting in T Cell Senescence and Human Immunodeficiency. Nature Immunology. 2014;15(1):88–97.
21. Walter, JE; Farmer, JR; Foldvari, Z *et al.* Mechanism-Based Strategies for the Management of Autoimmunity and Immune Dysregulation in Primary Immunodeficiencies. Journal of Allergy and Clinical Immunology: In Practice. 2016;4(6):1089-1100.

22. Jones, GL; Vogt, KS; Chambers, D *et al.* What is the Burden of Immunoglobulin Replacement Therapy in Adult Patients with Primary Immunodeficiencies? A Systematic Review. Frontiers in Immunology. 2018;9(1308):1–12.
23. Polverino, E; Goeminne, PC; McDonnell, MJ *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. European Respiratory Journal. 2017;50(3):1700629.
24. Pharming Data on File. Clinical Expert Perspective: Dr Chandra Questionnaire Responses. [Recieved: 25 November 2022] 2022.
25. Rao, VK; Webster, S; Dalm, V *et al.* Effective "Activated PI3Kδ Syndrome"-Targeted Therapy with the PI3Kδ Inhibitor Leniolisib. Blood. 2017;130(21):2307-2316.
26. Immunodeficiency UK. Immunoglobulin Therapy. Available from: https://mft.nhs.uk/app/uploads/sites/7/2018/04/Immunoglobulin-therapy-patientinformationsheet.pdf Last accessed: October 2022.
27. Mulder, FVM; Peeters, EFHI; Westerink, J *et al.* The long-term effect of mTOR inhibition on lipid and glucose metabolism in tuberous sclerosis complex: data from the Dutch TSC registry. Orphanet Journal of Rare Diseases. 2022;17(1):252.
28. Berglund, LJ. Modulating the PI3K Signalling Pathway in Activated PI3K Delta Syndrome: a Clinical Perspective. J Clin Immunol. 2023;44(1):34.
29. Pharming Data on File. Leniolisib Draft Summary of Product Characteristics (MHRA). 2024.
30. Rao, VK; Kulm, E; Sediva, A *et al.* Interim Analysis: Open-Label Extension Study of Leniolisib for Patients with APDS. Translational and Clinical Immunology. 2023;153(1):265-274.
31. Rao, VK; Webster, S; Šedivá, A *et al.* A randomized, Placebo-Controlled, Phase 3 Trial of PI3Kδ Inhibitor Leniolisib for Activated PI3Kδ Syndrome. Blood. 2023.
32. Pharming Data on File. Study 2201E1 CSR (IA2) and associated tables, figures and listings. 2023.
33. Pharming Data on File. A Survey of Physicians Treating APDS Patients with Leniolisib Through Early Access Supply/Program: A Semi-Quantitative Evaluation of Response to Treatment. Survey Report. 2024.
34. Rao K, ŠA, Bloomfield M, Kulm E, Webster S, Chong H, Bradt J, Uzel G. Assessing long-term treatment with leniolisib and its effects on bronchiectasis in patients with activated PI3Kδ syndrome (APDS). 2023. International Primary Immunodeficiencies Congress;
35. Michalovich, D; Nejentsev, S. Activated PI3 Kinase Delta Syndrome: From Genetics to Therapy. Frontiers in Immunology. 2018;9:369.
36. Orphanet. Activated PI3K-Delta Syndrome. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=397596. Last accessed: July 2022.
37. Pharming Data on File. ESID Registry Analysis of Individuals with APDS. Data to be Published. [Manuscript In Development]. 2023.
38. van der Maas, NG; Berghuis, D; van der Burg, M *et al.* B Cell Reconstitution and Influencing Factors After Hematopoietic Stem Cell Transplantation in Children. Frontiers in immunology. 2019;10:782-782.
39. Ogonek, J; Kralj Juric, M; Ghimire, S *et al.* Immune Reconstitution after Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2016;7:507.
40. Rao, VK; Kulm, EM; Grossman, JK *et al.* Long-Term Treatment With Selective PI3Kdelta Inhibitor Leniolisib in Adults With Activated PI3Kdelta Syndrome. Blood Adv. 2024.
41. Backeljauw, P; Cappa, M; Kiess, W *et al.* Impact of short stature on quality of life: A systematic literature review. Growth Horm IGF Res. 2021;57-58:101392.
42. Sowers, KL; Gayda-Chelder, CA; Galantino, ML. Self-reported cognitive impairment in individuals with Primary Immunodeficiency Disease. Brain, Behavior, & Immunity-Health. 2020;9:100170.
43. Matcham, F; Scott, IC; Rayner, L *et al.* The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. 2014. Seminars in arthritis and rheumatism;
44. Canetta, PA; Troost, JP; Mahoney, S *et al.* Health-related quality of life in glomerular disease. Kidney international. 2019;95(5):1209-1224.
45. Beh, SC; Greenberg, BM; Frohman, T *et al.* Transverse myelitis. Neurologic clinics. 2012;31(1):79.
46. Shvets, O; Rodina, J; Kann, N *et al.* Leniolisib in the treatment of pediatric patients with APDS: single center experience. 2024. 21st Biennial Meeting of the European Society for Immunodeficiencies; 16-19 Oct 2024.

47. Nijhof, LN; van Brussel, M; Pots, EM *et al.* Severe Fatigue Is Common Among Pediatric Patients with Primary Immunodeficiency and Is Not Related to Disease Activity. Journal of Clinical Immunology. 2021;41(6):1198-1207.
48. Zhang, S; Kline, M; Fuleihan, RL *et al.* PROMIS-29 survey confirms major impact of fatigue on health-related quality of life in common variable immunodeficiency. Immunologic Research. 2020;68(6):379-388.
49. Hitchcock, I; Skrobanski, H; Matter, E *et al.* A qualitative study to explore the burden of disease in activated phosphoinositide 3-kinase delta syndrome (APDS). Orphanet Journal of Rare Diseases. 2024;19(1):203.
50. Efthymiadou, O; Mossman, J; Kanavos, P. Health related quality of life aspects not captured by EQ-5D-5L: Results from an international survey of patients. Health Policy. 2019;123(2):159-165.
51. Pharming Data on File. Evaluating the Impact of Leniolisib Treatment on Symptoms and Health-Related Quality of Life (HRQoL) in Activated PI3Kδ Syndrome (APDS): [Accepted Abstract for EAACI 2024]. 2024.
52. Hajjar, J; Kutac, C; Henderson, TS *et al.* Predictors of fatigue in common variable immunodeficiency. Journal of Clinical Immunology. 2019;39:1-151.
53. Manusama, OR; M., NJ; van Beveren, N *et al.* Psychological Symptoms in Primary Immunodeficiencies: A Common Comorbidity? Journal of Clinical Immunology. 2022:695–698.
54. Genetic and Rare Disease Information Center (GARD). PALSI Disease. Available from: https://rarediseases.info.nih.gov/diseases/11983/pasli-disease. Last accessed: August 2022.
55. The Balancing Act, Y. Behind the Mystery of APDS: A Rare Primary Immunodeficiency. 2023. Available from: https://www.youtube.com/watch?v=R9w8Llmmr1w. Last accessed: January 2024.
56. Pharming Data on File. Ad-Hoc Expert Group Meeting Briefing Document. 2023.
57. Peasgood, T; Mukuria, C; Rowen, D *et al.* Should We Consider Including a Value for "Hope" as an Additional Benefit Within Health Technology Assessment? Value in Health. 2022;25(9):1619-1623.
58. Reed, SD; Yang, J-C; Gonzalez, JM *et al.* Quantifying value of hope. Value in Health. 2021;24(10):1511-1519.
59. Chen, G; Olsen, JA. Filling the psycho-social gap in the EQ-5D: the empirical support for four bolt-on dimensions. Qual Life Res. 2020;29(11):3119-3129.
60. Office for National Statistics. Employee earnings in the UK: 2024. 2024. Available from: https://cy.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2024. Last accessed: December 2024.
61. DKMS. UK's aligned stem cell registry reaches two million. 2024. Available from: https://www.dkms.org.uk/get-involved/stories/uk-s-aligned-stem-cell-registry-reaches-2-million. Last accessed: December 2024.
62. Büsch, 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. Advances in Therapy. 2024:1-20.
63. Thalhammer, J; Kindle, G; Nieters, A *et al.* Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. Journal of Allergy and Clinical Immunology. 2021;148(5):1332-1341.e1335.
64. Harrington, A, Malena Mahendran, Ramya Ramasubramanian, Heidi Memmott, Guillaume Germain, Katharina Büsch, François Laliberté. Overall survival among patients with Activated Phosphoinositide 3 Kinase Delta Syndrome. 2023. American College of Allergy, Asthma & Immunology (ACAAI) 2023 Annual Scientific Meeting;
65. Pharming Data on File. Private communication.
66. Genomics England Generation Study. Conditions we test for. 2024. Available from: https://www.generationstudy.co.uk/conditions-we-test-for. Last accessed: December 2024.
67. National Institute for Health and Care Excellence. Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (HST7). 2018. Available from: https://www.nice.org.uk/guidance/hst7. Last accessed: December 2024.
68. Limaye, S; Menezes, S; Hu, H *et al.* Leniolisib reverses pulmonary dysfunction and immune deficiency in activated phosphoinositide 3-kinase delta syndrome 1 (APDS1) – TheraPID Study. 2023. ASCIA 2023 Conference; 5th September 2023.
69. Klemann, C; Baumann, U; Renz, DM *et al.* Complicated course of activated PI3Kδ syndrome-1 (APDS-1) ameliorated by leniolisib: a case study. 2023. International Primary Immunodeficiencies Congress;

70. Tereza Lanitis, NM, Eszter Tichy. The Probability of a Successful Probabilistic Sensitivity Analysis. 2014. Available from: https://www.evidera.com/wp-content/uploads/2015/04/The-Probability-of-a-Successful-Probabilistic-Sensitivity-Analysis.pdf. Last accessed: June 2024.
71. [redacted]
72. Ara, R; Brazier, JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value in Health. 2011;14(4):539-545.
73. Costagliola, G; De Marco, E; Massei, F *et al.* The Etiologic Landscape of Lymphoproliferation in Childhood: Proposal for a Diagnostic Approach Exploring from Infections to Inborn Errors of Immunity and Metabolic Diseases. Therapeutics and Clinical Risk Management. 2024:261-274.
74. Pharming Data on File. Patient-reported outcomes and infection rates in patients with APDS: relationship with surrogate endpoints using clinical trial and registry data. 2024.

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Appendix A

A.1 IDUK survey: impact of APDS

Table 1: Results of IDUK survey on the impact of APDS on quality of life

Quality of life factor	Rating				Number of responses
	An extreme amount	A moderate amount	A little	Not at all	
Amount of tiredness experienced	3	7	2	1	13
The impact of being tired	2	4	6	1	13
Extent of worry about health	6	5	2	0	13
Worry about infections	11	1	1	0	13
Positivity about the future	2	4	5	0	11
Extent of enjoying life	4	5	1	2	12

Source: IDUK survey.[51]

A.2 Expert Gathering Exercise

The Expert Gathering exercise aimed to gather expert insights to inform this comment form and accompanying revised model base case. The exercise comprised of a questionnaire developed in SurveyMonkey (SurveyMonkey Inc., San Mateo, California, USA, www.surveymonkey.com), aiming to gather feedback and assumptions around the clinical plausibility of post-discontinuation return of manifestations and treatments scenarios, long-term benefits and uncaptured benefits of leniolisib, and to validate assumptions within the model and comment form.

Six clinical experts with expertise in APDS from the UK were asked to participate in the exercises. All six clinicians individually completed the questionnaire. The aggregated results are presented below in Table.

Table 2: Impact of manifestations on the daily living of individuals with APDS.

	No impact	Minimal impact	Moderate impact	Significant impact	Severe impact
Lymphoproliferation	0,00%	0,00%	83,33%	16,67%	0,00%
Infections	0,00%	0,00%	0,00%	100,00%	0,00%
Gastrointestinal manifestations	0,00%	0,00%	16,67%	50,00%	33,33%
Autoimmune cytopenias	0,00%	0,00%	50,00%	50,00%	0,00%
Bronchiectasis-associated airways disease	0,00%	0,00%	0,00%	83,33%	16,67%

Advanced lung disease	0,00%	0,00%	0,00%	33,33%	66,67%
Malignancies	0,00%	0,00%	0,00%	0,00%	100,00%
Hearing loss	0,00%	0,00%	33,33%	50,00%	16,67%
Antimicrobials	0,00%	33,33%	66,67%	0,00%	0,00%
IRT	0,00%	0,00%	100,00%	0,00%	0,00%
Immunosuppressive therapies (incl mTOR inhibitors)	0,00%	33,33%	66,67%	0,00%	0,00%
Corticosteroids	0,00%	16,67%	50,00%	33,33%	0,00%
HSCT	0,00%	16,67%	16,67%	33,33%	33,33%

Table 3: Risk of developing APDS clinical manifestations as patients age from infancy to adulthood.

Manifestation	Increases with age	No change	Decreases with age	Unsure
Developing lymphoproliferation	83,33%	16,67%	0,00%	0,00%
Infections	66,67%	16,67%	0,00%	16,67%
Developing gastrointestinal manifestations	66,67%	16,67%	0,00%	16,67%
Developing autoimmune cytopenias	66,67%	16,67%	0,00%	16,67%
Developing bronchiectasis-associated airways disease	100,00%	0,00%	0,00%	0,00%
Developing advanced lung disease	100,00%	0,00%	0,00%	0,00%
Developing malignancy	100,00%	0,00%	0,00%	0,00%
Developing hearing loss	33,33%	33,33%	16,67%	16,67%

Table 4: Clinically plausible scenarios of risk of return of manifestation after discontinuing leniolisib after 1, 5 and 10+ years for patients without the manifestation at treatment initiation and with the manifestation, which resolved/improved whilst on treatment

Discontinuation after number of years on leniolisib treatment		Higher risk than someone of the same age who did not receive leniolisib	Same risk as someone of the same age who did not receive leniolisib	The risk they had immediately before starting leniolisib	Start over with the risk of a newborn (i.e. starting from the beginning with APDS exposure)
Patients without the manifestation					
After 1 year	Lymphoproliferation	0,00%	40,00%	60,00%	0,00%
	Infections	0,00%	20,00%	80,00%	0,00%
	Gastrointestinal manifestations	0,00%	20,00%	100,00%	0,00%
	Autoimmune cytopenias	0,00%	40,00%	80,00%	0,00%

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	Bronchiectasis-associated airways disease	0,00%	20,00%	100,00%	0,00%
	Advanced lung disease	0,00%	20,00%	100,00%	0,00%
	Malignancy	0,00%	40,00%	80,00%	0,00%
	Hearing loss	0,00%	0,00%	80,00%	20,00%
After 5 years	Lymphoproliferation	0,00%	40,00%	60,00%	20,00%
	Infections	0,00%	20,00%	100,00%	0,00%
	Gastrointestinal manifestations	0,00%	20,00%	100,00%	0,00%
	Autoimmune cytopenias	0,00%	40,00%	80,00%	0,00%
	Bronchiectasis-associated airways disease	0,00%	20,00%	80,00%	20,00%
	Advanced lung disease	0,00%	20,00%	80,00%	20,00%
	Malignancy	0,00%	40,00%	80,00%	0,00%
	Hearing loss	0,00%	20,00%	80,00%	20,00%
After 10+ years	Lymphoproliferation	0,00%	40,00%	60,00%	20,00%
	Infections	0,00%	20,00%	100,00%	0,00%
	Gastrointestinal manifestations	0,00%	20,00%	100,00%	0,00%
	Autoimmune cytopenias	0,00%	40,00%	80,00%	0,00%
	Bronchiectasis-associated airways disease	0,00%	20,00%	80,00%	20,00%
	Advanced lung disease	0,00%	20,00%	80,00%	20,00%
	Malignancy	0,00%	20,00%	80,00%	20,00%
	Hearing loss	0,00%	20,00%	80,00%	20,00%
Patients with the manifestations, which resolved/improved while on treatment					
After 1 year	Lymphoproliferation	0,00%	40,00%	80,00%	0,00%
	Infections	0,00%	20,00%	100,00%	0,00%
	Gastrointestinal manifestations	0,00%	20,00%	100,00%	0,00%
	Autoimmune cytopenias	0,00%	40,00%	80,00%	0,00%

	Bronchiectasis-associated airways disease	0,00%	20,00%	100,00%	0,00%
	Advanced lung disease	0,00%	20,00%	100,00%	0,00%
	Malignancy	0,00%	20,00%	100,00%	0,00%
	Hearing loss	0,00%	20,00%	100,00%	0,00%
After 5 years	Lymphoproliferation	0,00%	50,00%	75,00%	0,00%
	Infections	0,00%	25,00%	100,00%	0,00%
	Gastrointestinal manifestations	0,00%	25,00%	100,00%	0,00%
	Autoimmune cytopenias	0,00%	50,00%	100,00%	0,00%
	Bronchiectasis-associated airways disease	0,00%	20,00%	80,00%	20,00%
	Advanced lung disease	0,00%	20,00%	80,00%	20,00%
	Malignancy	0,00%	50,00%	50,00%	25,00%
	Hearing loss	0,00%	20,00%	100,00%	0,00%
After 10+ years	Lymphoproliferation	0,00%	50,00%	50,00%	25,00%
	Infections	0,00%	25,00%	100,00%	0,00%
	Gastrointestinal manifestations	0,00%	25,00%	100,00%	0,00%
	Autoimmune cytopenias	0,00%	50,00%	50,00%	25,00%
	Bronchiectasis-associated airways disease	0,00%	20,00%	80,00%	20,00%
	Advanced lung disease	0,00%	20,00%	80,00%	20,00%
	Malignancy	0,00%	50,00%	50,00%	25,00%
	Hearing loss	0,00%	20,00%	80,00%	20,00%

Table 5: Level of agreement if immune reconstitution seen with leniolisib translates into long-term immune competence

	% Respondents
Strongly agree	0,00%
Agree	83,33%
Neither agree nor disagree	16,67%
Disagree	0,00%
Strongly disagree	0,00%

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Table 6: Level of impact of APDS patients initiating leniolisib treatment on the quality of life of caregivers.	% Respondents
1=Significant negative impact	0,00%
2=Slight negative impact	0,00%
3=No impact	0,00%
4=Slight positive impact	16,67%
5=Significant positive impact	83,33%

Table 7: Perceived mortality risk after discontinuing leniolisib following 1, 5 and 10+ years of treatment

Discontinuation after number of years on leniolisib treatment	Risk scenarios	Very plausible	Somewhat plausible	Not plausible
After 1 year of treatment	Higher than a person of the same age on standard care	0,00%	20,00%	80,00%
	The same as a person of the same age on standard care	33,33%	66,67%	0,00%
	Lower than a person of the same age on standard care	0,00%	100,00%	0,00%
After 5 years of treatment	Higher than a person of the same age on standard care	0,00%	0,00%	100,00%
	The same as a person of the same age on standard care	16,67%	83,33%	0,00%
	Lower than a person of the same age on standard care	40,00%	60,00%	0,00%
After 10+ years of treatment	Higher than a person of the same age on standard care	0,00%	0,00%	100,00%
	The same as a person of the same age on standard care	16,67%	66,67%	16,67%
	Lower than a person of the same age on standard care	80,00%	20,00%	0,00%

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Appendix B: Updated company base case and scenario analyses

In recognition of the committee's preferences, analyses requested within the Draft Guidance have been conducted.

Updated company base case

Pharming wishes to provide an updated company base case which incorporates the following changes and assumptions:

- Annual discount rates of 1.5% for both costs and health benefits. (A scenario analysis uses annual discount rates of 3.5% for costs and health benefits, per the committee's preference in the Draft Guidance)
- Sustained leniolisib benefit while on treatment (no change from the company submission base case, in line with the committee's preferred assumption)
- Leniolisib discontinuation rate of 2.7% per year based on continued follow-up in Study 2201E1 (May 2024 data cut) and the leniolisib EAP (28 Nov 2024 data cut). During 292 patient-years of treatment, there have been 8 discontinuations, giving an annual rate of 2.7%. (This is reduced from the 3.54% in the company submission base case, which was based on 7 discontinuations during 200 patient-years of treatment, using the March 2023 data cut of Study 2201 and 30 Jan 2024 data cut of the leniolisib EAP)
- The treatment-specific utility gain with leniolisib treatment has been removed (set to 0) in line with the committee's preferred assumptions. Pharming believes this change undervalues the utility benefits experienced by people treated with leniolisib, as described in Comment #4
- The baseline utility has been updated to [redacted], that of a [redacted] (instead of the company submission base case value of [redacted], calculated from clinician proxy responses to the EQ-5D). By using general population utilities, the model captures the full potential benefit of reducing disease-associated decrements, which might be underestimated by using the EQ-5D proxy utility values which already captured some of these decrements.[72] As the treatment-specific 0.1 utility gain is no longer used in the model, improvements in non-modelled manifestations such as fatigue are not valued, and should not be removed from the baseline utility. A scenario analysis with the proxy EQ-5D value used as the baseline utility is presented in Appendix B
- Standard error of 10% of the mean for model inputs without uncertainty information available (no change from the company submission base case)
- Structural alterations were made to the model to allow modelling of alternative scenarios around the return of manifestations and treatment use rates following discontinuation of leniolisib treatment. These changes are described in detail in Appendix C. In brief, for people who discontinued leniolisib, the annual risk of developing manifestations in the updated base case returned to the annual risk of current clinical management at the time of leniolisib initiation.

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- Survival on current clinical management is now based on a Weibull distribution fit to survival data in the latest ESID registry dataset (26 November 2024). (The company submission base case used data extracted from a systematic literature review; however, analyses of the latest ESID registry dataset indicate that survival on current clinical management has previously been overestimated; see comment #5 and Appendix C)

- The impact of leniolisib on survival is calculated based on a 1.77% reduction in survival versus the general population. In the Expert Consultancy (presented in the original company submission, Section B.3.3.4. "Impact of leniolisib on survival"), clinicians indicated that responders to leniolisib would be expected to have similar survival to the general population. With almost 400 patient-years of leniolisib treatment across Study 2201, the leniolisib EAP, and US post-marketing experience, only 3 deaths have been reported, giving a mortality rate of less than 0.8% per year. Patient experience on leniolisib in Study 2201 and the EAP was compared with expected mortality rates in the general population for the same age and duration of follow-up, to estimate the 1.77% reduction (see Appendix C for details)

- The HR for incidence of malignancy while on leniolisib is 0.53, based on (i) the annual risk of developing malignancy of 1.3% under current clinical management, using an exponential distribution fit to the Kaplan-Meier curve for 'any malignancy' from the APDS cohort in the ESID registry, and (ii) the annual probability of developing malignancy when receiving leniolisib is estimated to be approximately 0.7%, based on two reports of malignancy (neither case associated with leniolisib)[32, 65] over 291.9 patient-years of leniolisib treatment in Study 2201 and the EAP. This is a slight reduction from the HR of 0.55 in the company submission base case, based on the latest available data

- The HR for incidence of lymphoproliferation while on leniolisib is 0, based on no reports of persistent lymphoproliferation in Study 2201 or the EAP survey. This is a reduction from the HR of 0.42 in the company submission base case, based on the latest available data; please see Appendix C for details

- An updated PAS of [redacted] for leniolisib has been submitted to NHSE and NICE, bringing the price per pack cost of treatment to [redacted]

The results of the updated company base case are presented in Table 8 (deterministic), Table 9 and Figure 3 (probabilistic). In the deterministic analysis, leniolisib was associated with a weighted ICER of £[redacted]/QALY. After alterations to the model structure to incorporate tunnel states, and subsequent error checking, the probabilistic and deterministic analyses provide similar results in the revised model, probabilistic results were well aligned with the deterministic results.

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Table 8: Deterministic base-case results, with QALY weighting (with proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Undiscounted incremental QALYs[a]	Discounted incremental QALYs[b]	Weighted incremental QALYs[c]	ICER[b] (£/QALY)	Weighted ICER[c] (£/QALY)
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	12.06	21.71	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							

Footnotes: [a]The number of "Undiscounted incremental QALYs" was used to determine the weight to be assigned to the QALY benefits. [b]The "Discounted incremental QALYs" and "ICER" columns are presented for the committee to see the economic results without QALY weighting. [c]The "Weighted incremental QALYs" and "Weighted ICER" columns apply the weighting determined by the number of undiscounted incremental QALYs.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 9: Probabilistic base-case results, with QALY weighting (with proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Undiscounted incremental QALYs[a]	Discounted incremental QALYs[b]	Weighted incremental QALYs[c]	ICER[b] (£/QALY)	Weighted ICER[c] (£/QALY)
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17.99	12.03	21.64	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							

Footnotes: [a]The number of "Undiscounted incremental QALYs" was used to determine the weight to be assigned to the QALY benefits. [b]The "Discounted incremental QALYs" and "ICER" columns are presented for the committee to see the economic results without QALY weighting. [c]The "Weighted incremental QALYs" and "Weighted ICER" columns apply the weighting determined by the number of undiscounted incremental QALYs.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 3: Scatterplot of probabilistic results (unweighted, with proposed PAS)

Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Scenario analyses

A number of scenario analyses were conducted.

1. Use of a 3.5% discount rate applied to both costs and benefits, in line with the committee's preferred assumptions
2. Post-discontinuation probabilities (see Appendix C for details):
    a. Manifestation and treatment probabilities are set equal to that of current clinical management, for the age of discontinuation
    b. Manifestation and treatment probabilities return to the risk at age 0 for bronchiectasis, advanced lung disease, and malignancy, while other probabilities are set equal to that of current clinical management, for the age of discontinuation
    c. Manifestation and treatment probabilities are temporarily higher in the leniolisib arm post-discontinuation than in the current clinical management arm, in order to ensure return to the lifetime risk on current clinical management. This applies to patients treated for <10 years of leniolisib. Patients return to the lifetime risk of current clinical management within 1 year if discontinuation happens in the first year of leniolisib therapy
3. Baseline utility based on proxy clinician EQ-5D survey
4. Survival using the company submission base case approach (literature estimates and leniolisib HR)

Results of the scenario analyses are presented in Table 10 and Table 11. For all results, leniolisib has been included at updated, proposed PAS price and the comparator at list prices. QALY-weighted ICERs ranged from £[redacted] to £[redacted] per QALY gained, indicating that the updated base case ICER is robust to the varied assumptions, including those where exploration of uncertainty was requested by the NICE committee.

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Table 10: Deterministic scenario analysis results (with QALY weighting and proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Undiscounted incremental QALYs[a]	Discounted incremental QALYs[b]	Weighted incremental QALYs[c]	ICER[b] (£/QALY)	Weighted ICER[c] (£/QALY)
Updated base case										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	12.06	21.71	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 1. Discount rate of 3.5% applied to costs and benefits (comment #5)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	7.80	14.05	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 2a. Post-discontinuation risk equal to current clinical management (comment #2)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.99	12.45	23.64	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 2b. Post-discontinuation risk mix of current clinical management and young age (comment #2)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20.30	13.24	26.88	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 2c. Post-discontinuation risk returning to lifetime untreated risk (comment #2)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17.43	11.62	20.25	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 3. Baseline utility from EQ-5D clinician survey										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.77	11.23	18.84	[redacted]	[redacted]

Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 4. Survival based on company submission base case										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.06	10.85	17.43	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							

Footnotes: [a]The number of "Undiscounted incremental QALYs" was used to determine the weight to be assigned to the QALY benefits. [b]The "Discounted incremental QALYs" and "ICER" columns are presented for the committee to see the economic results without QALY weighting. [c]The "Weighted incremental QALYs" and "Weighted ICER" columns apply the weighting determined by the number of undiscounted incremental QALYs.

Table 11: Probabilistic scenario analysis results (with QALY weighting and proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Undiscounted incremental QALYs[a]	Discounted incremental QALYs[b]	Weighted incremental QALYs[c]	ICER[b] (£/QALY)	Weighted ICER[c] (£/QALY)
Updated base case										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17.99	12.03	21.64	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 1. Discount rate of 3.5% applied to costs and benefits (comment #5)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	7.79	14.02	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 2a. Post-discontinuation risk equal to current clinical management (comment #2)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19.01	12.46	23.69	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 2b. Post-discontinuation risk mix of current clinical management and young age (comment #2)										

Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20.31	13.24	26.90	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 2c. Post-discontinuation risk returning to lifetime untreated risk (comment #2)										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17.47	11.63	20.31	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 3. Baseline utility from EQ-5D clinician survey										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.85	11.28	19.01	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							
Scenario 4. Survival based on ACM1 base case										
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.14	10.89	17.59	[redacted]	[redacted]
Current clinical management	[redacted]	[redacted]	[redacted]							

Footnotes: The base case probabilistic analysis was run with 10,000 simulations. The mean incremental costs / incremental QALYs changed <0.001% for 100 consecutive simulations for the first time at simulation #3714. Therefore, all scenario analyses below have been run with 5,000 simulations. [a]The number of "Undiscounted incremental QALYs" was used to determine the weight to be assigned to the QALY benefits. [a]The number of "Undiscounted incremental QALYs" was used to determine the weight to be assigned to the QALY benefits. [b]The "Discounted incremental QALYs" and "ICER" columns are presented for the committee to see the economic results without QALY weighting. [c]The "Weighted incremental QALYs" and "Weighted ICER" columns apply the weighting determined by the number of undiscounted incremental QALYs.

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Appendix C: Details of changes to the ACM1 model base case

This Appendix provides details of four changes to the model base case from ACM1:

1. Structural alterations to explore post-discontinuation risk of manifestations and treatment
2. Survival on current clinical management
3. Impact of leniolisib on survival
4. Hazard ratio of 0 for incidence of lymphoproliferation during leniolisib treatment

C.1 Structural alterations to explore post-discontinuation risk of manifestations and treatment

The company submission used a three-stage model ("alive on leniolisib", "alive on current clinical management" and "dead") to estimate outcomes on leniolisib treatment. In the "alive on current clinical management" health state, the model applied the average annual incidence rate of manifestations and treatments, which was a simplifying assumption to manage the various risks for people who had discontinued leniolisib after 1 year, or 20 years, but were now in the same health state. The Committee requested exploration of alternative scenarios for the returning risk of manifestations and current treatments following discontinuation of leniolisib.

The leniolisib arm of the revised model includes "alive on leniolisib" and "dead" health states, as before. The "alive on current clinical management" health state has been replaced by 20 different health states, which represent people who are alive after discontinuing leniolisib during Year 1 of therapy, Year 2, Year 3, and so on, with a final health state capturing all people who discontinue leniolisib during Year 20+ of therapy. All "alive" health states separately model the proportions of patients with manifestations and treatment use.

In the Expert Gathering exercise, 6 clinicians were asked to rate the plausibility of post-discontinuation risk return scenarios, separately for (i) people who did not have a specific manifestation at baseline and then discontinued after 1, 5, or 10+ years of leniolisib, and (ii) for people who did have a specific manifestation at baseline and then discontinued after 1, 5, or 10+ years. The majority of responses (≥50%) indicated that it would be most plausible for the risk to return to the risk faced prior to starting leniolisib. Responses were consistent for people without the manifestation at baseline (60% of responses for lymphoproliferation, 80–100% of responses for all other manifestations) regardless of the duration of leniolisib treatment prior to discontinuing. For people with a manifestation at baseline, who experienced improvement or resolution of the manifestation on leniolisib treatment but discontinued within one year, 80–100% of responses indicated that it would be most plausible for the risk to return to that in the year prior to initiating leniolisib. For people who discontinued after 5–10 years of leniolisib, while 50–100% of responses indicated returning to the risk in the year prior to leniolisib would be most plausible, 20–25% of responses indicated it would be most plausible to return to the risk in a newborn for manifestations including lung disease, malignancies, cytopenia and hearing loss, while 20–50% thought that risk could be equal to that on current clinical management at the same age. Importantly, no clinician responded that risk would be higher than on current clinical management, indicating that a "catch-up" function may not be clinically plausible.

Experts were also asked if manifestation risks would ever catch up to that of current clinical management, for people who discontinued leniolisib after long-term therapy (10+ years) (Appendix A). One expert believed that it is plausible to return to current clinical management risk, while 83% responded that it is "not plausible" for lymphoproliferation and malignancy, and 50% responded "not plausible" for infections, gastrointestinal manifestations and bronchiectasis. Over 50% of respondents viewed return to current clinical management risk as either "not plausible" or "somewhat plausible".

Considering responses to the Expert Gathering exercise, in the first year post-discontinuation, the updated base case applies a manifestation risk equal to that they had immediately before leniolisib initiation on current clinical management . For example, the risk of developing persistent lymphoproliferation is 6.25% for a 15-year old receiving current clinical management. If a patient in the leniolisib arm discontinues, their risk of developing lymphoproliferation in the next year will be 6.25%, regardless of their age or time on leniolisib. In the second year post-discontinuation, the manifestation risk of a 16-year old (3.33%) will be applied, in the third year post-discontinuation, the risk of a 17-year old (6.9%) will be applied, and so on until the end of the time horizon.

For scenario analysis, the model includes other options for modeling post-discontinuation risk:

- A second option is to return to the risk of a newborn (i.e. age 0–1) for the first year post-discontinuation, age 1–2 for the second year post-discontinuation, and so on

- A third option is to apply an age-specific current clinical management risk; for example, a patient who discontinues leniolisib at age 24, will in the next cycle be subject to the risk of manifestations and treatments of a 25-year-old on current clinical management

- A fourth option is a catch-up function which applies an annual risk of developing manifestations that is higher than that observed on current clinical management, in order to return the manifestation and treatment prevalence to that on current clinical management. The rate of catch-up is equal to the time spent on therapy; i.e. someone who discontinues after 1 year of leniolisib therapy returns to manifestation prevalence on current clinical management within one year post-discontinuation. Someone who discontinues after 6 years of leniolisib therapy returns to current clinical management manifestation prevalence within 6 years post-discontinuation. This continues up to year 10, at which point patients who discontinue return to the risk of their starting age, consistent with the base case. The annual risks in this scenario are multiples of what are normally observed without leniolisib treatment; for example, a base-case patient who discontinues leniolisib after 3 years will be subject to annual risks of lymphoproliferation of 43%, for three years (from age 18). The average annual risk for people with APDS who never received leniolisib, is approximately 6% for ages 18–21

C.2 Survival on current clinical management

The economic analysis in the company submission considered survival based on a review of published cases. Survival estimates obtained in this way are subject to a number of biases which are likely to overestimate life expectancy for the wider APDS population, as described in comment #5.

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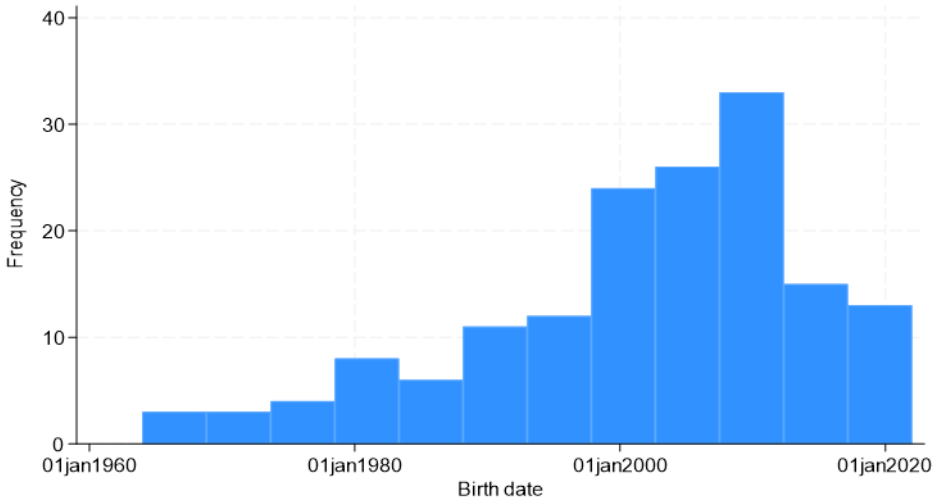
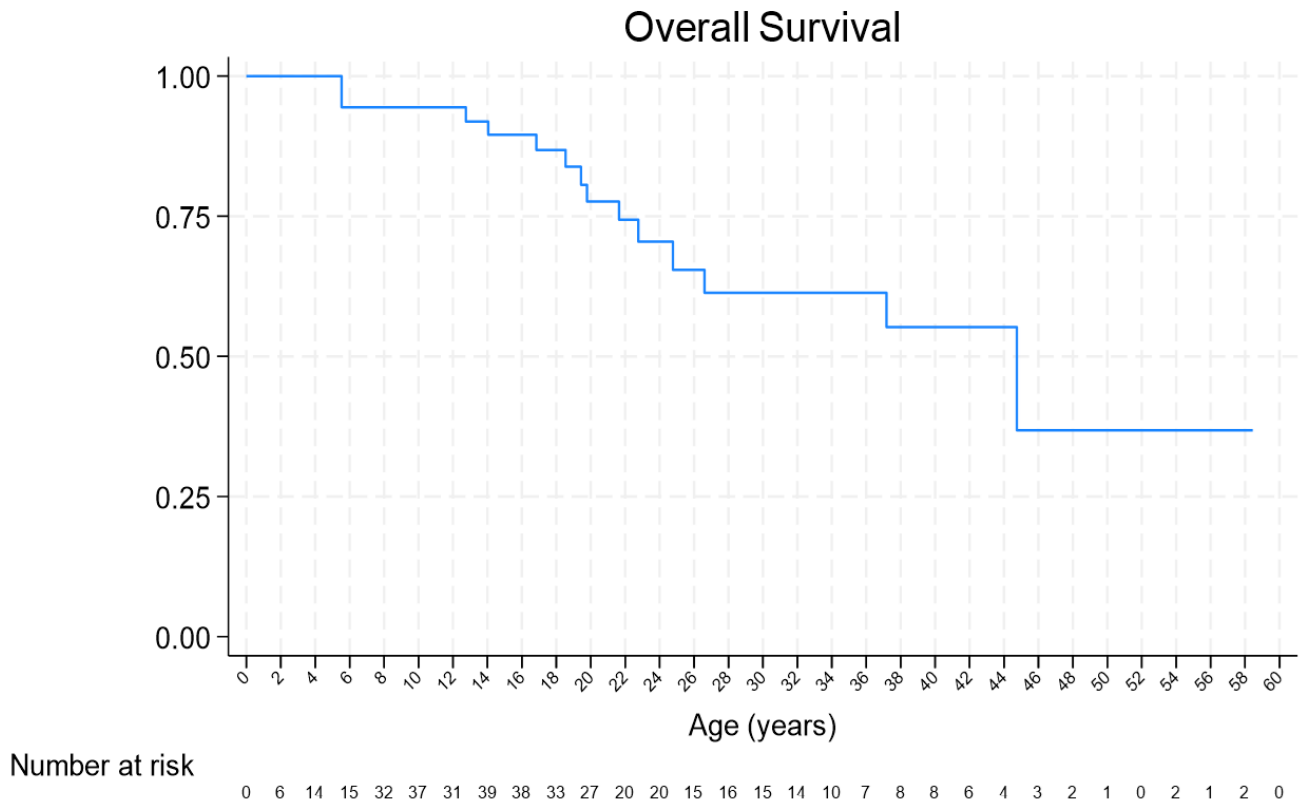
The ESID registry includes a date of registration and consent to participate, and includes a median (range) of 4.7 (<1 to 18.4) years of follow-up. Mean (SD) age at registration was 15.7 (11.8) years old. Kaplan-Meier analysis of overall survival was conducted using age as the time scale, and defining the at-risk period from the age of registration to the age of death or last follow-up (censor). Birth date was imputed as 1st January of the year of birth for all 158 patients. Age of entry to the analysis was imputed by (start of follow-up date – birth date + 1 day)/365.25 days, while age at the end of follow-up was imputed by (end of follow-up date – birth-date + 1 day)/365.25 days. 13 deaths occurred during follow-up. The below images present the histogram of birth dates (indicative of a relative lack of known people with APDS in their fourth or later decade of life) and the results of the Kaplan-Meier analysis.

Figure 4: Histogram of birth dates of the APDS cohort in the ESID registry (November 2024 cut-off)



Source: Pharming Data on File, 2024.[10]

Figure 5: Kaplan-Meier curve of overall survival of the APDS cohort in the ESID registry (November 2024 cut-off)



Source: Pharming Data on File, 2024.[10]

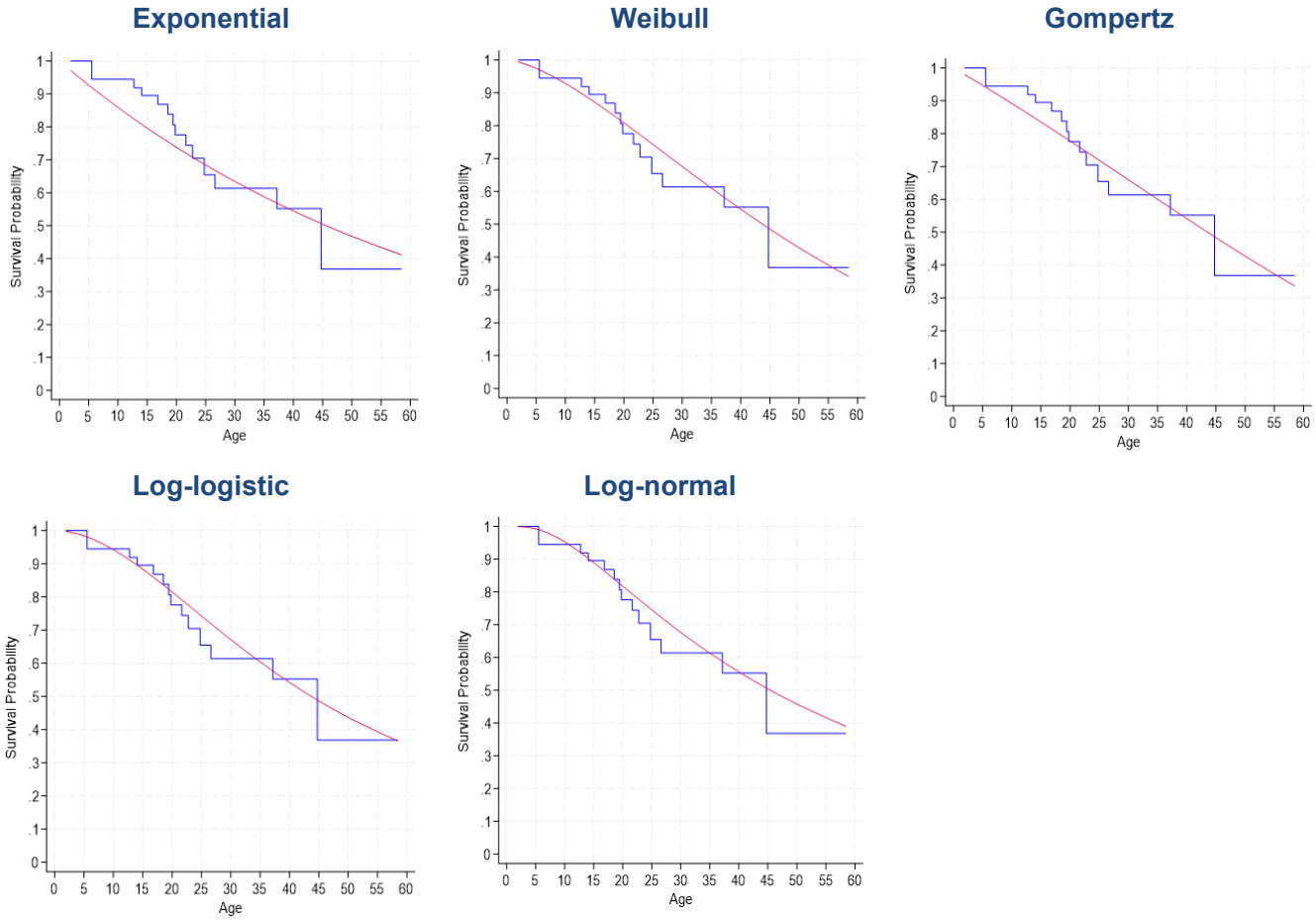
Parametric models were fit to the survival data, to facilitate use in the economic model. Parameters and fit statistics are presented in Table 12, as well as visual plots in Figure 6. The base case uses a Weibull distribution to model survival on current clinical management.

Table 12: Parametric curve fit for overall survival data from the APDS cohort in the ESID registry

Parameter	Fitted parametric distributions				
	Exponential	Weibull	Gompertz	Log-logistic	Log-normal
λ	0.0151839	1.51151	0.0104188	0.02286498	
p		0.0022932			
γ			0.0182412	0.5278267	
μ					3.816214
σ					0.9054688
AIC	59.47109	60.28489	60.87815	59.83884	59.89616
BIC	62.52094	66.3846	66.97786	65.93855	65.99587

Abbreviations: AIC: Akaike Information Criterion, AIC: Bayesian Information Criterion, OS: overall survival.

Figure 6: Parametric curve fit for overall survival data from the APDS cohort in the ESID registry



Source: Pharming Data on File, 2024.[10]

C.3 Impact of leniolisib on survival

Achieving immune reconstitution and competence should significantly reduce or eliminate the excess mortality associated with APDS. In the Expert Consultancy (presented in the original company submission, Section B.3.3.4. "Impact of leniolisib on survival"), multiple HCPs indicated that responders to leniolisib would be expected to have similar survival to the general population. With almost 400 patient-years of leniolisib treatment across Study 2201, the leniolisib EAP and US post-marketing experience, only 3 deaths have been reported, giving a mortality rate of <0.8% per year.

To calculate the reduction in survival versus the general population, the age of leniolisib initiation, number of years of treatment, and outcome at last exposure were collected for 125/128 patients in the Study 2201E1 and EAP (as patient-level data were not available for US post-marketing experience). The 3/128 excluded patients were in the EAP and had no age information available. The median (IQR) age at treatment initiation was 17 (11, 26) years and follow-up was 1.8 (0.8, 3.5) years, with 10% of patients having more than five years of follow-up. Two people died during follow-up.

English life tables were used to calculate the probability of death for equivalent patients, based on age and duration of follow-up. For example, a 24-year old person with 7 years of follow-up would have a [redacted]% probability of survival. Across the entire age- and follow-up-matched population in Study 2201 and the EAP, expected survival would be [redacted]% for the general population versus [redacted]% survival observed in people treated with leniolisib. This corresponds to a survival likelihood of [redacted]% for people treated with leniolisib, versus the general population. The calculation was re-done to weight each patient by their years of follow-up, resulting in a survival likelihood for people treated with leniolisib of [redacted]% that of the general population. This value was used in the model base case.

C.4 Hazard ratio of 0 for incidence of lymphoproliferation during leniolisib treatment

The company submission described a single event of persistent lymphoproliferation observed during Study 2201E1; however Pharming believes this was a transient event (as explained below) and was improperly included as an event in our efficacy calculations. Therefore, there has been no development or recurrence of persistent lymphoproliferation while on leniolisib therapy.

[redacted][73].

[redacted]

- [redacted]
- [redacted][74] [redacted]

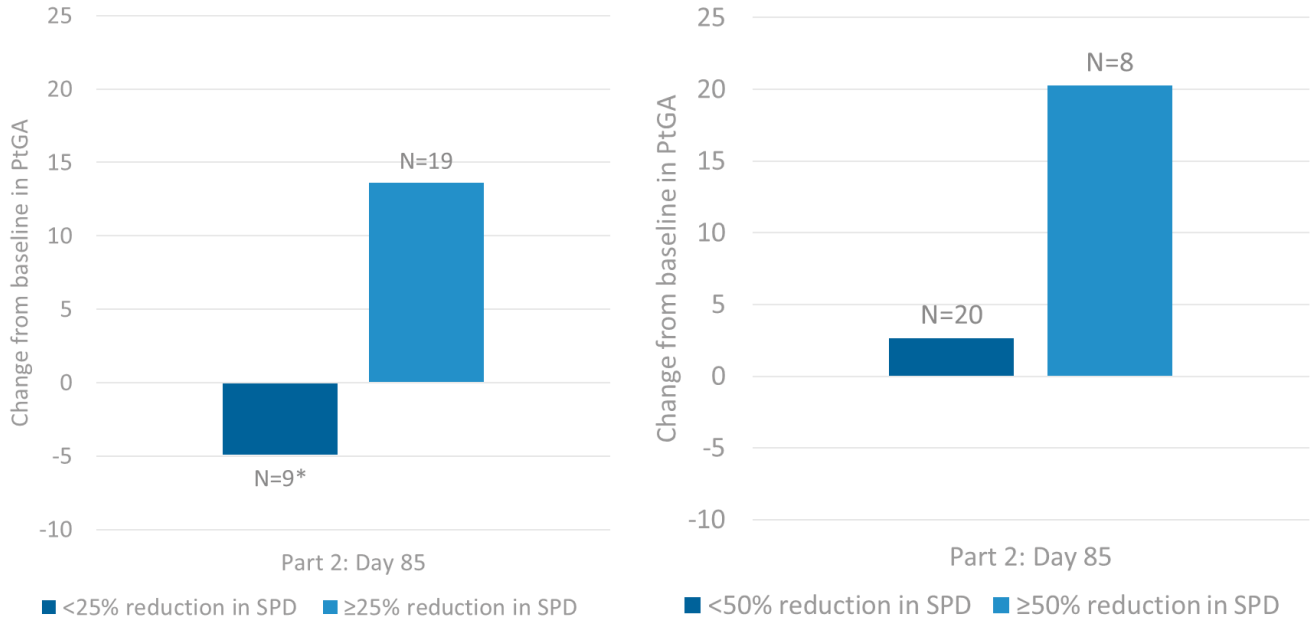
Table 13: PtGA scores at each visit (scores can range from 0 "very poor" to 100 "very good")

Day	D1	D29	D57	D85	ExD176	ExD253[a]	ExD336	ExD440	ExD521
PtGA score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Extension imaging visit
Abbreviations: D: Study 2201 Part II visit, days since treatment initiation; ExD: Study 2201E1 visit, days since treatment initiation; PtGA: patient global assessment.

- [redacted]
- [redacted]

Figure 7: Change from baseline in PtGA and index lymph node SPD during Study 2201 Part II



Footnotes: *8 placebo patients and one leniolisib patient. The leniolisib patient had a 24.98% reduction in SPD and a 41-point improvement in PtGA.
Abbreviations: PtGA: patient global assessment; SPD: sum of product of diameters.

NICE National Institute for Health and Care Excellence

Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over [ID6130]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **21 November 2024**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Immunodeficiency UK

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], Immunodeficiency UK.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Overall, we are concerned that this initial NICE decision infers that the drug Leniolisib will be not be made available to people affected by APDS. Access to innovative treatments is a fundamental part of the UK Rare Disease Action Plan. This is the only drug that addresses the fundamental cause of APDS and we are pleased that NICE agrees (page 8 'there is an unmet need for an effective treatment that addresses the cause of APDS').
2	We have been asked to specifically comment on the impact of caring for someone with APDS: The impacts reported to the charity are on physical, mental health and quality of life. Carers report stress and anxiety, difficulty with sleeping, depression, feelings of isolation; fears about the future. Dealing with the emotional distress of the affected child/adult. Extra stress is caused by managing treatment, hospital appointments, dealing with unexpected hospital admissions; dealing with schools explaining periods of absence; continually explaining the condition to others. Carers report an inability to hold down a job or having to take reduced working hours leading to financial instability for the family; an inability to socialise with families leading restrictive lifestyles not being able to carry out normal family activities and hobbies. Carers reported an impact on unaffected siblings in terms lack of time to spend with them due to caring for an affected child or adult. As this is a genetic disorder people with APDS may be looking after their affected children so will be struggling with their own health problems as well as the responsibilities of caring.

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	Quotes from carers: 'Tough, exhausting'. 'It's stressful.' 'Emotionally distressing.' 'I'm worried all the time.' 'Concerns about [their] development both socially and academically.' 'The amount of hospital appointments and providing medical care each week at home'. '2-3 physio sessions a day, medicine administered daily, weekly subq infusions, frequent soiling as on antibiotics regularly'. 'delayed development so not potty trained and can't wash himself.' 'Unable to work and socialise. Tired and lack of sleep. Difficult to maintain routine.' 'I have to provide help with day-to-day activities.' 'Significantly, my mother had to give up work, family holidays had to be cancelled, hobbies for my siblings had to be cancelled, time my parents spent with my siblings was compromised as they were always with me.' 'I am unable to work due to xxx's condition as she is constantly getting infections and needs iv medication at least 2/3 monthly', 'Mindful of no soft plays, limit to parks and long walks.' 'Disproportionately caring for child with APDS over other children, lots of holiday from work spent hospital admissions, days work around physio'. 'We all have to know about it, the younger sibling has to fit around the treatment, we have to pay extra for travel insurance, we have to be more conscious of infection, we have to fit in hospital appointments and medical supplies ordering.' .
3.	Page 18 Concerning the emotional benefit of having the drug – the emotional toll on patients and carers of having APDS would be reduced due to the drug causing direct improvements in health such as reduced number of infections, reduced treatment burden, increased energy, increased ability to socialise and have a normal family life.

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	These would be in addition to reducing fears about future health risk of developing lymphoma.
4	Page 20 states 'Many new and existing treatments provide increased hope…'. This is a sweeping statement and unsubstantiated. We ask NICE to validate this statement by defining the 'many new' [treatments] as we are not aware of other new drugs that specifically target the defect in APDS.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHSE Immunology and Allergy CRG

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the impact of the evidence (i.e.. the significance of positive phase 3 studies) has not been adequately explored with regards the potential to reduce the overall therapeutic burden and associated costs to the NHS and reduction in morbidity to the patient.
2	We are concerned that the economic model by the committee has been rejected based on an assumption re: treatment failure that is not borne out by the known science (this is not cancer, which was alluded to, but there is no likelihood of "Escape" mutations, since the therapy removes selective advantage).
3	We are concerned that the economic model is focussed on discontinuation and failure in a way that is not equitable with other settings. For e.g. drugs in Hereditary Angioedema (HAE) there was no requirement to demonstrate higher costs by remaining on therapy if it fails. The other therapies (e.g. in HAE such as Berotralstat) are required to be monitored and discontinued if ineffective. This therefore appears to have introduced an inequality dependent on the genetic diagnosis/rare disease.
4	There was no detailed acceptance of the potential reduction in costs of Intravenous Immunoglobulin (IVIG)/Subcutaneous Immunoglobulin (SCIG) which is an important high cost drug in these patients.

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5	We are concerned that the outcome of this appraisal suggests that patients should continue on high cost drugs e.g. IVIG and use off-licence therapies (e.g. Sirolimus, which also has a significant cost) where a licenced targeted therapy is available. The purpose of the genetics programme in the NHS is to identify in rare disease treatable subsets with cleaner targeted therapies and this outcome suggests that patients will not be able to access such treatments unless they can demonstrate a higher than usual level of adherence to meet a funding model that is preferred by NICE but with no evidence of greater relevance in this setting.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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EAG response to company draft guidance response

EAG executive summary response

In October 2024, the National Institute for Health and Care Excellence (NICE) issued a Draft Guidance Consultation (DGC) for leniolisib for untreated activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over.[1] The DGC states leniolisib is not recommended within its marketing authorisation, for treating APDS in people 12 years and over at the moment due to the uncertainties in the economic modelling around how best to model the effect of stopping treatment.[1] The NICE stressed a number of key issues on the clinical and cost effectiveness of leniolisib compared with standard of care (SoC).

In December 2024, the company submitted a response to the NICE DGC.[2] The responses include comments attempting to address six key concerns raised by the committee in the DGC: (a) Lifelong treatment effect assumed; (b) treatment discontinuation rate and the manifestations and treatment reoccurrence rates after discontinuation; (c) additional utility gain and the uncaptured leniolisib benefits; (d) 1.5% non-reference case discount rate and (e) standard error assumption in the probabilistic sensitivity analysis. The company also provided a revised economic model attempting to address the uncertainties mentioned in the DGC.

Overall, the EAG acknowledge the effort the company has made to incorporate updated data inputs as well as improve the explanatory power of the model by adding leniolisib treatment discontinuation groups by time on treatment. The EAG believe that the implementation of these treatment discontinuation groups is correct. The EAG has no concerns about its implementation aside from the minor issues on pages 8 and 9 (Section 3). The EAG also think that the assumptions in the revised model are mostly aligned with the committee's suggestions in the DGC. However, as the EAG still think that the company provided insufficient evidence to support the claim of using a different annual discount rate for costs and health benefits, we apply a 3.5% discount rate for costs and health benefits in the EAG base case, which is consistent with the committee's suggestion in the DGC.[1]

The EAG also constructed additional scenarios to investigate the impacts of alternative mortality rates, alternative hazard ratios (HR) or treatment waning on the cost effectiveness results. The EAG base case and scenario analyses are detailed in the EAG's analysis section below. The probabilistic results show that the preferred assumptions in the EAG base case increase the weighted ICER by [redacted] compared with the revised CS base case ([redacted] vs [redacted]). The deterministic results show a similar story - the preferred assumptions in the EAG base case increase the weighted ICER by [redacted] compared with the revised CS base case ([redacted] vs [redacted]). The previous issue of the gap between deterministic and probabilistic results has been resolved in the revised model.

For the EAG scenarios, reproduction of company scenario 2c using the adjusted manifestation-specific mortality rates based on the ESID data has the largest effect on ICER among all EAG scenarios, with the ICER increased by [redacted], to [redacted] compared with the EAG base case. The scenario with the second largest impact on the ICER is the manifestation-specific mortality rates adjusted based on the ESID data (ICER increased by [redacted], to [redacted]).

All the EAG's comments to the new company submission (CS) are detailed in the response to specific company's comments below.

EAG critique of company DGC response

Lifelong treatment effect assumed

EAG Response: In the original CS, the company stated that the benefits of lenolisib are expected to remain the same over a lifetime of taking the treatment based on the claim that no clear mechanism for people to develop resistance to leniolisib.[3] The EAG in the original report stressed that there was no long-term data beyond 6 years to support the assumption of sustained efficacy over time. The committee concluded that the assumption was plausible based on the mechanism of action, "but it would consider this uncertainty in its

decision making."[1] In company's comments to the DGC, the company provided additional clinical evidence that no discontinuation has been observed among "20 patients with APDS have received >4 years of leniolisib therapy", implying that "no long-term need for rescue medications or alternate therapies due to a treatment waning effect."[2] Taking into account of the committee's preference and the company's clarification based on the current clinical evidence, the EAG think that the assumption of the sustained treatment effect is plausible. However, to aid committee's decision making, the EAG explored alternative scenarios where treatment waning under different magnitude in the EAG's additional scenario analysis section (Scenario 10 and Scenario 11).

Treatment discontinuation rate

1. Discontinuation rate

In the Section 3.11 of the DGC, the committee preferred using the company's discontinuation rate based on observed clinical and real-world data in the economic model, which is 3.54%.[1] In the responses to the DGC, the company updated their discontinuation rate based on the most recent follow-up studies. The new discontinuation rate is now 2.7%, and it is used in the updated company's base-case model.[4] Taking into account the committee's preference and the company's evidence, the EAG think that the discontinuation rate based on the new real-world evidence is plausible.

2. Manifestation and treatment recurrence rates

In the previous economic model, patients were modelled that they would return to manifestation rates and treatment use under the SoC after discontinuing from the leniolisib based on limited real-world evidence. The company assumed a constant linear increase rate (equal to the annual rate of manifestation/treatment use under the SoC) for each manifestation and treatment use until fully returning to the SoC rates.[3] In the DGC, the committee commented that the rate of return of manifestations and treatment use to SoC may depend on (a) how long someone had spent on treatment, (b) the type of manifestation, and (c) potentially the age at which they started treatment. The committee mentioned that the previous assumption on the return rate was lack of evidence and face validity (e.g., it takes years for patients to return to SoC in a scenario of 100% discontinuation rate after 1 year on treatment) and questioned whether it has been implemented correctly in the model.[1] Given the existing the possible errors, the committee suggested the model being checked by a statistician, yet the EAG notice that the company did not explicitly responded to this request. The new model has been checked by the EAG's senior modeller and have found no obvious errors with the implementation of treatment discontinuation, application of the alternative manifestation returning rates and the calculation of cumulative incidence curves. However, there was an uncertainty regarding how the manifestation hazard ratios were calculated. The EAG modeller also spotted an error in the company. Please see discussion under the title "Cumulative risk calculations checked by EAG senior health economist" in the EAG response below.

The also committee provided the following suggestions: (a) the return rate to be modelled in a way so that the probability of developing a manifestation each year after stopping treatment follows the hazard rate of the cumulative incidence functions from age 0 (i.e., newborn); (b) adjust the hazard rate of infections to reflect lower risks in older people; (c) adjust the hazards for duration of treatment; (d) explore a conservative scenario that models an immediate return to SoC rates of manifestations and treatment use.[1]

In response to the DGC, the company updated the model structure by adding treatment discontinuation groups by time on treatment, enabling it to separately model post-discontinuation events for patients discontinuing in the first 20 years.[2] The company explored different scenarios of manifestation and treatment recurrence rates based on evidence from an Expert Gathering Exercise.[2] In the exercise, six UK-based clinical experts in APDS were asked to state their views on the expectation of the return of manifestations and treatment use after discontinuing from leniolisib for 1, 5, or 10+ years.[5] Based on clinicians' opinions, the company explored the following four scenarios in the models, with the first scenario (most plausible based on clinical experts' opinions) being the base case in the revised CS model and the rest of the three scenarios explored in scenario analyses:

- New CS base case: manifestations rates return to the risks before starting leniolisib treatment regardless of age and time on treatment (e.g., the manifestation rate for lymphoproliferation is 6.25% for a 15-year old person receiving SoC, then his/her risk of having this manifestation in the next year would be 6.25% if discontinued in the first year, and 3.33% in the second year of post-discontinuation, and 6.9% in the third year of post-discontinuation, and so on until the end of the time horizon).
- CS Scenario analysis 2a: apply age-specific current clinical management risk (e.g. if a patient discontinues leniolisib at age 20, his/her risk of manifestations and treatments in the next cycle would be equal to the one under SoC for a 21-year old).
- CS Scenario analysis 2b: manifestations rates return to the levels of a new-born (i.e. age 0–1) for the first year post-discontinuation, age 1–2 for the second year post-discontinuation, and so on).
- CS Scenario analysis 2c: a temporarily higher risk than the SoC so it can "catch up" rates under SoC, with the returning rate calculated so that the time to return of SoC manifestation prevalence is equal to the length of time on treatment for those discontinued within ten years (e.g. someone who discontinues after 6 years of leniolisib therapy returns to SoC manifestation prevalence within 6 years post-discontinuation). For those treated more than ten years, patients who discontinue return to the risk of their starting age (i.e., consistent with the base case).

The base-case results from the company show that the unweighted (i.e., without applying a QALY weight) ICER for the leniolisib intervention compared with the SoC is [redacted] (weighted ICER is [redacted]) in the deterministic analysis and [redacted] (weighted ICER is [redacted]) in the probabilistic analysis. The unweighted ICER for the alternative scenarios regarding manifestation and treatment use returning rates (Scenario 2a -Scenario 2c) ranges from [redacted] to [redacted] (weighted ICER ranges from [redacted] to [redacted]) in the deterministic analysis and from [redacted] to [redacted] (weighted ICER ranges from [redacted] to [redacted]) in the probabilistic analysis. The company then concluded they "considered that the impact of the associated uncertainty is small" after examining different clinically plausible post-discontinuation risks.[2]

The EAG notice that the assumptions of these scenarios are largely based on the answers from the Expert Gathering Exercise done by the company and reported in the company's response to the DGC.[2] During the consultation process for the development of the ECM1 report, the EAG asked their clinical experts to comment on the most plausible treatment discontinuation rate and treatment waning effects. The clinicians advised that they were unable to provide any estimates due to the lack of long-term data. The EAG have not able to approach a clinical expert to comment on the most appropriate return to manifestation risk after receiving company's revised model due to time constraints. As, the EAG has not obtained any clinical evidence in addition to company's expert's opinion, the EAG rely on the results from the Expert Gathering Exercise and think that the return to manifestation rates applied in the company's revised base case is the most appropriate option given the available evidence.

For the previous model, the issue of face validity was raised by the committee in Section 3.11 of the DGC when the discontinuation rate was assumed as 100%.[1] The company's Scenario 2c of the updated model seems to address this issue. In this case, the manifestation rates jump back to those under the SoC within one year, with a QALY gain of [redacted], consistent with the model assumption. However, the EAG concern that the base-case and the other scenarios on alternative returning rate assumptions (i.e., CS Scenario 2a and 2b) still have this issue. For example, in a base-case scenario with an assumption of a 100% discontinuation in the first year, the manifestation rate for Lymphoproliferation needs 20+ years to "catch up" the rate under the SoC, resulted in a QALY gain of [redacted]. Therefore, the EAG think that the issue of face validity of the model pointed by the committee still exists.

The company declined several scenarios mentioned in the DGC based on the answers from the Expert Gathering Exercise: (a) lower infection risk as age increases; (b) an immediate return to standard care rates of manifestations and treatment use. For (a), the company argued that most clinical experts agreed that the risks of developing infections and some other manifestations increase with age, and therefore this scenario is not plausible and not considered in the analysis. For (b), the company clarified that the expert declined the plausibility of the scenario in which the risk in the year post-discontinuation would be higher than that of

someone under SoC, and therefore an immediate return of risk to SoC was not modelled, but a similar scenario with a more "gentle" assumption on the returning rate was explored in CS Scenario 2c.

Overall, the EAG acknowledge that the company has attempted to address the concerns regarding manifestation risk after treatment discontinuation following the committee's suggestions. Specifically, the scenario analyses allow for the manifestation and treatment use returning rates to be dependent on age or treatment length, which address some of the concerns raised by the committee in Section 3.11 of the DGC. Regarding the sustained QALY benefit following 100% discontinuation rate, the EAG think that it depends on the assumptions of returning rates of manifestations the company made and the different disutility values associated with the manifestations modelled by the company. It is intuitive that the sustained QALY benefit will disappear when immediate returns (i.e., very high returning rates) are assumed, and the sustained QALY benefit will exist when gradual returns are assumed. Therefore, the EAG think that the "sustained QALY benefit" issue is more relevant to the assumptions of returning rates and assumed disutility values, rather than error in model implementation. Additionally, the EAG note that the sustained QALY benefit following 100% discontinuation can also be amplified by the large disutilities associated with some manifestations that are relatively large, e.g., Gastrointestinal. These disutilities diminish or disappear when patients are on Leniolisib contributing to the sustained QALY benefit when patients return to gradually experiencing manifestations upon treatment discontinuation.

The EAG think that "which rates of return to manifestations are plausible" is a clinical question. The clinical evidence from the Expert Gathering Exercise conducted by the company is the only available clinical evidence directly related to the rates of return to manifestations. The evidence suggests that returning to the risk before leniolisib initiation (company's revised base case) is the most plausible scenario and returning to lifetime risk (company scenario 2c) is the least plausible scenario. Specifically, company's scenario 2c implies "catch-up" risks higher than the risks of manifestations of the same age under SoC in the first few years after discontinuation, which is against the experts views submitted by company (see Table 4 of Appendix A in the company's response[2]). The EAG also notice that in the DGC, the committee asked to test this immediate return to SoC rates as a conservative scenario.[1]

Regarding the sustained QALY effects for 100% discontinuation after first year, the EAG notice that there is no evidence suggesting it is clinically implausible. In addition, the company provided evidence suggesting that some patients can get treatment benefit immediately after having leniolisib. For example, the company stated in the CS that "the annualised infection rate decreased to 1.962 (previous leniolisib) and 1.444 (previous placebo) during the first year of leniolisib exposure (DCO: 13th March 2023)."[3]

Based on the argument above, the EAG think that returning to the risk before leniolisib initiation (company's revised base case) is the most plausible scenario and use it as the returning rates for EAG base case.

Removal of additional utility gain of 0.1

See EAG's response to comment wider, uncaptured benefits of leniolisib treatment.

Wider, uncaptured benefits of leniolisib treatment

The company removed the 0.1 utility gain from the revised model as part of the new evidence submission, in line with committee's suggestions. However, the company claimed that not accounting for benefits not explicitly incorporated into the model may underestimate the real benefits of leniolisib. In the new CS, the company provided a wider discussion on the potential uncaptured benefits of leniolisib treatment on the following aspects: (a) reduce fatigue, (b) reduce emotional distress, (c) increase hope, (d) increase QoL of caregivers and families, (e) educational, societal and inequality.[2]

However, the EAG think that these effects may have been captured by the existing treatment effect on the reduction of manifestations rates through the included utility estimates in the model, which is consistent with the committee's view mentioned in Section 3.12 of the DGC.[1] In addition, the company did not supply

sufficient evidence to reasonably quantify the additional benefits mentioned in the new evidence submission. Therefore, whilst the EAG acknowledge the possibility of some additional benefits of leniolisib not incorporated in the model, the additional utility of 0.1 is not recommended due to lack of distinction and quantification of these additional effects and is not included in the EAG base case.

On a related issue, the company used a new baseline utility value (i.e., [redacted]) instead of [redacted] in the previous model. The new baseline utility was sourced from [redacted] [6] As stated in the EAG report, proxy EQ-5D values were not the preferred source of utility. There is an argument that if it is not reasonable to assume a 0.1 utility decrement associated with having the condition without leniolosib and without manifestations, then a general population utility may be applicable for the same state. In addition, both company's scenario analysis (company scenario 3) and EAG's own analysis (not reported in the response doc) suggest that the impact of using alternative baseline utility is not sufficiently large to raise concern. Overall, the EAG think that it is reasonable to assume the utility of an APDS patient without manifestations close to that of a same-age person from the general public.

1.5% non-reference case discount rate

The committee in the DGC mentioned that there is no evidence showing that most of the manifestations can be fully resolved after having leniolisib treatment, and that permanent damages caused by the previous manifestations can be reserved by having leniolisib (so this does not meet Criterion 2: it is likely to restore them to full or near-full health).[1] Although the committee generally acknowledged the substantial negative effect of APDS on QoL, they mentioned that this effect can be heterogenous (so this does not meet Criterion 1: The technology is for people who would otherwise die or have a very severely impaired life).[1]
In the new CS, the company mentioned that the committee has accepted the company met Criterion 3 (i.e., the benefits are likely to be sustained over a very long period) for using a 1.5% annual discount rate for health benefits and cost. The EAG agrees with the company's interpretation and thus think that the company has met Criterion 3. The company provided further rebuttals on how the technology met Criterion 1 and Criterion 2.

For Criterion 1, the company stated that NICE Topic Selection and Oversight Panel (TSOP) has previously acknowledged that the QoL of the majority of people with APDS will be severely affected, yet as no reference was provided, the EAG could not assess the validity of the statement. Other evidence from a sample of 60 patients suggested a high lifetime risk of severe diseases such as malignancy was also mentioned.[7] The company then illustrated how they met Criterion 1 by discussing possibilities of APDS's heterogeneous effects on QoL for some patients, including experiencing disease manifestations prior to diagnosis and potentially underestimating survivals from the current literature. The company also suggested that almost all manifestations of APDS have severe or significant impacts on QoL based on clinical experts' opinions,[7] and over half of the mid-age APDS patients had experienced at least one severe.[8] The company also argued that APDS patients are more likely to be diagnosed when they have already shown symptoms of manifestations, and therefore "any shift in heterogeneity is likely to skew toward the severe end of the disease spectrum".[2]

For Criterion 2, the company stated that short-term immune restoration due to having leniolisib treatment could lead to long-term immune efficiency based on clinical experts.[5] They also mentioned that in HST7, "the committee was reassured by clinical experts that short-term immune reconstitution, leading to long-term immune competence, was expected to enable patients with ADA-SCID (also a combined immunodeficiency) to achieve normal or near-normal health",[2] yet the EAG notice that the committee for HST7 finally concluded that "it was uncertain about whether Strimvelis fully met the criteria to use a discounting rate of 1.5%".[9] The company also highlighted two cases on which individuals with APDS initially showed severe manifestations and restored to "full health" after having leniolisib.[10-11] The EAG is not able to extract the evidence, and thus could not evaluate the results of the cited references. The EAG think that a larger sample of patients who restored to full health is needed to strengthen the claim.

Overall, the EAG thinks Criterion 1 has been met. For Criterion 2, the EAG acknowledge that some evidence from the trial and observational data signal the likelihood of patients returning to near-full health for some

patients, likely for those who are at the early stage of APDS, yet the EAG is uncertainty the current evidence is sufficient to support the claim the technology is likely to restore the patients to full or near-full health. Therefore, the EAG still use the 3.5% discount rate for both costs and health benefits in the EAG base case, as preferred by the committee.

Model uncertainty – probabilistic sensitivity analysis

Following committee's acknowledgement in the DGC, the EAG thinks the assumption of the 10% standard error in the PSA (probabilistic sensitivity analysis) is plausible. The company stated that the difference in ICER results between the probabilistic and deterministic analyses disappeared after incorporating treatment discontinuation groups and subsequent error checking.[2] The EAG acknowledge the company's effort to fix this issue, yet in replying to the committee's request that "what factors were driving the difference between the deterministic and probabilistic cost-effectiveness estimates".[1] the company should provide the reason or a list of reasons for the occurrence of the issue, and how these issues were addressed. In addition, the company used 10,000 iterations for their PSA, implying a significant amount of computational effort. However, the EAG found that the issue of the significant gap between the deterministic and probabilistic results has been resolved in the revised model with 1,000 iterations of PSA run. The EAG use 1,000 iterations in their probabilistic analysis as it is sufficient to produce unbiased results.

The EAG initially was not able to verify the company's probabilistic results due to (an) error(s) in the company's revised model in the PSA sheet: the cost- effectiveness results are the same across all simulation iterations after running the PSA (this should not be the case, as each time a probabilistic data input drawn from a distribution should be different, resulting in different cost effectiveness results). After a corrected version was supplied by the company, the EAG was able to produce their own probabilistic results.

Cumulative risk calculations checked by EAG senior health economist

1. Cumulative incidence changes to the company model

Changes were made regarding the following:

- SoC manifestation incidence estimates
- Effectiveness estimates in reducing the rate of manifestations
- The interpretation and calculation of cumulative incidence curves for SoC and Leniolisib

2. Changes to the company's calculation of cumulative incidence curves for SoC and Leniolisib

2.1. SoC

The company presents the annual incidence data for standard care estimated from the ESID registry. In the original model this was interpreted as the difference in cumulative incidence $(CI\_SoC_t - CI\_SoC_{t-1})$.
In the new model this has been reinterpreted as annual incidence I_SoC_t, where it is calculated based on the at-risk population at the start of each annual period.
Note that:

$$I\_SoC_t = \frac{CI\_SoC_t - CI\_SoC_{t-1}}{1 - CI\_SoC_{t-1}}$$

Original model

$$CI\_SoC_t = CI\_SoC_{t-1} + (CI\_SoC_t - CI\_SoC_{t-1})$$

New Model

$$CI\_SoC_t = CI\_SoC_{t-1} + (1 - CI\_SoC_{t-1}) \times I\_SoC_t$$

Definitions:
CI_SoC_t: the proportion of people receiving SoC who have a specific manifestation in time period t
CI_SoC_{t-1}: the proportion of people receiving SoC who have a specific manifestation in time period $t-1$
I_SoC_t: the annual incidence of a specific manifestation based on the at-risk population at the start of each period

Original model SoC cumulative incidence equation
Manifestations!AB29=MIN(**(AB28+F29)***INDEX(p_age_manifes,AB$26),MaxInc)

New model SoC cumulative incidence equation
Manifestations!AC31=MIN(**(AC30+(1-AC30)*F31)**,MaxInc)

2.2. Leniolisib

The company changed the calculation of the cumulative incidence of manifestations for those receiving leniolisib.
The new model accounted for the different interpretation of the incidence data: $(CI\_SoC_t - CI\_SoC_{t-1})$ and I_SoC_t. This required multiplying the at-risk population in those receiving leniolisib at the start of each annual period by I_SoC_t: $(1 - CI\_L_{t-1})$.
Original model

$$CI\_L_t = CI\_L_{t-1} + (CI\_SoC_t - CI\_SoC_{t-1}) \times Red\_rate$$

New Model

$$CI\_L_t = CI\_L_{t-1} + (1 - CI\_L_{t-1}) \times I\_SoC_t \times Red\_rate$$

Definitions:
CI_L_t: the proportion of people receiving leniolisib who have a specific manifestation in time period t
CI_L_{t-1}: the proportion of people receiving leniolisib who have a specific manifestation in time period $t-1$
CI_SoC_t: the proportion of people receiving SoC who have a specific manifestation in time period t
CI_SoC_{t-1}: the proportion of people receiving SoC who have a specific manifestation in time period $t-1$
Red_rate: the effectiveness estimate (probably a risk ratio- see Section 3.3)
I_SoC_t: the annual incidence of a specific manifestation based on the at-risk population at the start of each period

Original model
Manifestations!P44=IF($O44=StartAge,AB44*(1-INDEX(ResolutionMani,P$26)),IF($O44>StartAge,P44+ **(AB44-AB43)***INDEX(ReduRateMani,P$26),AB44))
New model
Manifestations!Q46=MIN(MaxInc,IF($P46=StartAge,AC46*(1-INDEX(ResolutionMani,Q$28)), IF($P46>StartAge,Q45+**(1- Q45)*F46***INDEX(ReduRateMani,Q$28),AC46)))

3. Commentary

3.1. Interpretation of annual incidence data

The EAG cannot comment on how the incidence data should be interpreted as the company has not presented the methods used to calculate them. We must rely on the company description of the data, which has changed from the original model to the new model.

3.2. Calculation of cumulative incidence for leniolisib

The EAG considers the original calculation of the cumulative incidence for leniolisib to be incorrect. This is due to the fact that the effectiveness estimate was multiplied by $(CI\_SoC_t - CI\_SoC_{t-1})$ rather than I_SoC_t. However, based on the reinterpretation of the incidence data and the change to the calculation of cumulative incidence for leniolosib, the EAG considers the calculation in the new model to be correct with only one caveat regarding the effectiveness estimate (see Section 3.3).
The difference between the old and new methods of calculating the cumulative incidence curves for leniolisib is greatest when the percentage resolution is high and there is a significant manifestation rate reduction (but not 100%) associated with leniolisib. The manifestation where the difference would have been greatest is lymphoproliferation, but the hazard ratio for leniolosib is now assumed to be 0 in the new model, meaning that the there would be no difference in the cumulative incidence curve for the two methods.

3.3. The interpretation and application of the reduced rate of manifestations

It is not entirely clear from the company submission whether the hazard ratio was calculated directly or whether a risk ratio was used as a proxy for the hazard ratio. Technically, the best approach is to calculate the hazard ratio using the risk ratio and the baseline risk and then derive the annual rates and risks for leniolisib for each year given that the baseline risk changes year-on-year. However, the risk ratio may be a reasonable approximation to the hazard ratio.
If a hazard ratio was estimated then the calculations in the model are not technically perfectly correct as further transformations of the data are required.
If the risk ratio was used as a proxy for the hazard ratio (which may be the case) then the application in the new model is correct.

3.4. Implementation of manifestation rates for those who have discontinued leniolisib

In the original model, while manifestation incidence rates vary by year in the calculation of cumulative incidence curves for people receiving SoC or leniolisib, the simplification of using the average incidence rate across years is used when calculating the cumulative incidence curves for those who have discontinued leniolisib. The EAG acknowledges this as a pragmatic approach, but it can significantly alter the manifestation cumulative incidence curves for patients who have discontinued leniolisib. The degree to which it affects the manifestation cumulative incidence curves for the whole starting leniliolisib cohort depends on the discontinuation rate and therefore the percentage of patients who have discontinued leniolisib at any specific period of time.

In the new model, patients are assumed to experience the annual-specific manifestation risks, which vary significantly from year-to-year.

3.5 Likely error in the cumulative incidence calculations of infections off-leniolisib

The following applies to the new model.

For several leniolisib treatment discontinuation groups, in the new model for Scenario 2c, where the manifestation cumulative incidence rebounds to SoC cumulative incidence, the cumulative incidence of infections for people off-leniolisib is slightly lower than that for those on-leniolisib. This suggests an error in the equation. It arises because a constant risk probability per cycle is applied and it is capped at the SoC cumulative incidence, but the SoC infection manifestation cycle-specific risk is sometimes zero. However, the EAG has not corrected this error due to the late stage in was identified. Additionally, the difference is at most 0.005 over a range of cycles, and therefore should not have any significant effect on the results.

In the leniolisib engine in the leniolisib treatment discontinuation groups, there is a possible error in the calculation of the bronchiectasis-associated airway disease at age 26 where the sum of the cumulative incidence proportions of people with bronchiectasis-associated airway disease and advanced lung disease is less at age 26 than at age 25. However, this issue was discovered late. In the SoC engine, the incremental advanced lung disease is subtracted from the increase in the bronchiectasis-associated airway disease proportion. But that in itself does not explain how you could have a reduction year-on-year in the sum of the

two. However, the difference is only -0.005 and the EAG does not expect this to have a significant impact on the results.

EAG additional analyses

EAG base-case (ECM2)

Based on the considerations discussed in the company's responses to the draft guidance and the revised model, the EAG base case included an adjustment to the company's revised base case. This adjustment is based on matters of judgement.

As the EAG believes that the revised company model generally provides better explanatory power, the revised EAG base case for ECM2 is based on the company's revised model, yet with the following corrections:

- **The EAG applied a 3.5% discount rate for both the costs and health effects, as opposed to 1.5% discount rate**
- **Following the EAG base case for ECM1, the EAG used an updated list of the unit costs applied to the economic model.**

(a) The assumption of the discount rate applied to both costs and health effects

As detailed in the response to Comment #5, the EAG acknowledge the potentially large positive impact of leniolisib on the improvement of QoL and life expectancy of people with APDS, yet whether most of the patients can return to near-full health after the treatment remains uncertain. Therefore, the EAG applied a 3.5% discount rate for both the costs and health effects in the revised EAG base-case analysis for ECM2. Consequently, the in the company's revised model file ("ID6130 Leniolisib CEM 121224IM [CON]"), was changed as follows: The value in "Setting" Sheet, Cell K25 and K26, was changed from 1.5% to 3.5% for the base-case.

(b) The list of unit costs

As stated in the submitted ECM1 EAG report, the EAG were not able to verify some of the unit costs submitted by the company. The list of the unit costs applied to the economic model can be found in Appendix 1 of the EAG report for ECM1.

Please note that in the revised EAG base case for ECM2, the EAG applied the data inputs preferred by the committee following suggestions from the ECM1 and the DGC, including: (i) treatment discontinuation rate provided by the company (2.7%), (ii) 10% standard errors in probabilistic sensitivity analysis. The EAG also note that one of the errors identified by the EAG in the previous model (i.e., the calculation of the age-weighted unit cost; see the second point of Fixing Errors in the EAG report, p.99) has been corrected by the company in the revised company model. The EAG agree with the correction.

EAG exploratory scenario analyses

The EAG performed the following scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

Mortality data

The EAG have specific comments on the use of alternative mortality data for current clinical management. The company's previous mortality of people with APDS under the SoC is based on a review of published cases.[12] The company acknowledged that these estimates may subject to several biases, including censoring the dead patients (i.e., only surviving patients were reported), which could underestimate the mortality. In the revised model, up-to-date mortality data from the ESID registry were used to construct the Kaplan-Meier

curve for the APDS patients, and the fitted parametric curve following a Weibull distribution was used in the model. The EAG generally think the company's use of the ESID registry data as primary source is appropriate and acknowledge the potentially less biases of the new source. However, the EAG is little concerned that the ESID registry contains 158 patients, whilst the sample size of the previous mortality data is larger (i.e., 351 individuals).

The EAG is also concerned that the APDS-specific mortality is not linked to the manifestations in the model. The intuition is that patients with more manifestations should have higher mortality rates, which is not reflected in the model using the APDS-specific mortality. Furthermore, any scenario that changes the risk of manifestations should also affect model survival predictions. In the company base case, mortality is modelled independently of manifestation risk. Therefore, the EAG explores the impacts of the mortality data source and reproduces the company scenarios that affect manifestation risk using the manifestation-specific mortality rates.

Manifestation-mortality rates

There are two sources of survival data for APDS: in the original company submission the survival curve was derived from the Hanson et al. (2024) case series;[12] in the latest submission, the survival curve was derived from the ESID registry data. In the company submission, the company calibrated the manifestation-specific mortality rates so that the model survival predictions better matched the Hanson case series. The EAG has done its own calibration of the model so that the manifestation-specific survival curve matches as far as reasonably possible the early part of the SoC curve based on the ESID registry survival data (EAG Scenario 1, calibration factor = [redacted]), and the early part of the SoC curve based on the Hanson case series survival data (EAG Scenario 2, calibration factor = [redacted]). Note that the EAG's calibration does not attempt to match the whole SoC curve as the predicted part of the curve exhibits more uncertainty. The calibration factor matches the calibration factor in the company submission based on the Hanson case series, which also prioritised calibration with the early part of the cohort survival curve. In the manifestation-specific scenario constructed by the company, it does not appear that mortality is set to be the general population mortality rates when these are greater than estimated APDS mortality rates, whereas this is done for scenarios with ESID 2024 mortality rates. Figure 1 accounts for general population mortality rates, but the EAG has not had time to edit the model to provide these results in a timely manner. A limitation of this approach is that the model predicted survival curve for SoC using the manifestation-specific mortality rates may overestimate survival in the short-term and underestimate survival in the long-term.

The model-predicted survival curve based on manifestation-specific hazard rates is compared with the ESID 2024 Kaplan-Meier curve and the predicted ESID 2024 cohort survival curve in Figure 1. The model-predicted survival curves for leniolisib were assumed to vary if the manifestation risk and incidence curves varied in the scenario analyses, and these scenario leniolisib survival curves are also presented in Figure 1. The leniolisiib survival curves do not vary significantly between scenarios. Malignancies and Advanced lung disease are associated with the greatest mortality. These are conditions that have a higher risk at older ages; consequently, the scenario (Leniolisib 2b) that returns manifestation risk to that of the newborn is associated with the most favourable survival curve.

Figure 1: Model survival curves for leniolisib assuming fixed cohort survival and manifestation-specific mortality rates

Leniolisib base case: Return to starting age manifestation risk & manifestation-specific mortality rates
Leniolisib 2a: Current age SoC manifestation risks & manifestation-specific mortality rates
Leniolisib 2b: Return to newborn manifestation risks for long-term conditions and current age SoC manifestation risks for other manifestations & manifestation-specific mortality rates
Leniolisib 2c: Catch-up to SoC cumulative manifestation incidence based on the duration of treatment & manifestation-specific mortality rates
APDS on leniolisib: the survival curve for those patients who stay on leniolisib for a lifetime derived from the ESID 2024 data and a hazard ratio for leniolisib versus SoC
APDS cohort leniolisib: the survival curve for the entire leniolisib cohort derived from the ESID 2024 data and a hazard ratio for leniolisib versus SoC
ESID 2024: the Kaplan-Meier curve for SoC from ESID data
APDS cohort SoC (ESID 2024): the fitted curve for SoC to the ESID data
SoC manifestation-specific: the SoC survival curve using manifestation-specific mortality rates, calibrated to the early part of the ESID survival data (calibration factor=[redacted], the same as used by the company)

To assess how the change of mortality rates affect the return rates after treatment discontinuation, the EAG produce the following scenarios: the EAG Scenarios 3-5 are reproductions of the company scenarios 2a, 2b and 2c using the EAG base case, and the EAG Scenarios 6-8 are the are reproductions of the company scenarios 2a, 2b and 2c using the manifestation-specific mortality rates adjusted based on the mortality sourced from the ESID registry data.

Hazard ratios

The EAG is generally positive about the revision of the hazard ratio (HR) for the incidence of lymphoproliferation and malignancy given the explanation provided by the company. However, the EAG test the impact of the change of HR for lymphoproliferation and malignancy in the EAG's additional scenario (Scenario 9) given the large difference in magnitude between the revised and original HR for lymphoproliferation. The EAG use the original (i.e., 0.42 and 0.55) instead of the revised (i.e., 0 and 0.53) HRs for the incidence of lymphoproliferation and malignancy in EAG Scenario 9.

Treatment waning effect

As detailed in Comment #1, the EAG consider a waning effect of 10% in EAG Scenario 10 and 20% in EAG Scenario 11, both happened at the fifth year after having leniolisib (i.e., at Age 20) following a common assumption made in the tests of treatment waning in health technology assessment.[13] This is achieved by modifying the HRs in incidence rate for the manifestations, so that the HRs are increased by 10% (Scenario 10) or 20% (Scenario 11) compared with the original set of HRs. Note that revised HRs were not allowed to exceed 1.

EAG scenarios

(1) Assuming manifestation-specific mortality rates adjusted based on the mortality sourced from the ESID registry data, as opposed to APDS-specific mortality rates sourced from the ESID registry data
(2) Assuming manifestation-specific mortality rates adjusted based on the mortality sourced from the hanson et al. (2024), as opposed to APDS-specific mortality rates sourced from the ESID registry data
(3) Reproduction of company scenario 2a using the EAG base case
(4) Reproduction of company scenario 2b using the EAG base case
(5) Reproduction of company scenario 2c using the EAG base case
(6) Reproduction of company scenario 2a using the manifestation-specific mortality rates adjusted based on the mortality sourced from the ESID registry data
(7) Reproduction of company scenario 2b using the manifestation-specific mortality rates adjusted based on the mortality sourced from the ESID registry data
(8) Reproduction of company scenario 2c using the manifestation-specific mortality rates adjusted based on the mortality sourced from the ESID registry data
(9) Assuming original hazard rates for the for the incidence of lymphoproliferation and malignancy (i.e., 0.42 and 0.55), as opposed to the revised hazard rates (i.e., 0 and 0.53)
(10) Assuming a 10% waning effect happened at Year 5 after having leniolisib treatment, as opposed to no waning effect
(11) Assuming a 20% waning effect happened at Year 5 after having leniolisib treatment, as opposed to no waning effect

Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

EAG base case analysis

The results of the deterministic and probabilistic analyses for the EAG base-case are presented in Table 1. Both incremental costs and QALYs are deflated compared with the revised CS base case. This is expected as the only change the EAG made in the base case was to change the discount rate from 1.5% to 3.5%. As the undiscounted QALY gain from the preferred EAG base-case analysis is [redacted], which is between 10 to 30, a QALY gain weight will be applied met on this occasion. The weighted ICER in the deterministic EAG base case is [redacted] ([redacted] for the unweighted ICER), as opposed to [redacted] ([redacted] for the unweighted ICER) in the revised CS base case, suggesting a [redacted] increase.

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined effect of uncertainty from parameter precision on the results of the cost-effectiveness analysis. Following the committee's suggestions, we used a 10% standard error assumption for parameters where empirical probability distributions were not available. The PSA was run for 1,000 iterations.

The cost-effectiveness plane and acceptability curves are presented in Figure 2 and Figure 3, respectively. These results use the proposed PAS price for leniolisib and the list prices for the comparator. The results show that leniolisib was associated with a [redacted] probability of being cost-effective at a £100,000/QALY willingness-to-pay (WTP) threshold, without QALY weighting, or a [redacted] probability of being cost-effective at a £100,000/QALY threshold with QALY weighting. The probabilistic results were aligned with the deterministic base case results, indicating that the base case ICER is robust to uncertainty in parameter precision.

Table 1: Deterministic EAG base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Unweighted ICER (£/QALY)	Weighted ICER (£/QALY)
Revised CS base-case – deterministic									
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	12.06	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]						
Revised CS base-case – probabilistic									
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17.99	12.03	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]						
Revised CS base-case (after fixing errors) – deterministic									
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	12.06	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]						
Revised CS base-case (after fixing errors) – probabilistic									
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.00	12.05	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]						
EAG base-case – deterministic									
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.01	7.80	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]						
EAG base-case – probabilistic									
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17.97	7.77	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]						

Source: EAG outputs
Abbreviations: EAG = Evidence Assessment Group; ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Figure 2: Scatterplot of probabilistic results (with unweighted QALYs)

Figure 3: Cost-effectiveness acceptability curves (with unweighted QALYs)

EAG scenarios

Table 2: EAG scenario analysis results

Scenario #	EAG base-case input	Alternative input	Incr. costs (£)	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Weighted ICER (£/QALY)
	EAG base-case (deterministic)	N/A	[redacted]	18.01	7.80	[redacted]

Scenario #	EAG base-case input	Alternative input	Incr. costs (£)	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Weighted ICER (£/QALY)
	EAG base-case (probabilistic)	N/A	[redacted]	17.97	7.77	[redacted]
1	APDS-specific mortality rates based on the ESID data	Manifestation-specific mortality rates adjusted based on the ESID data	[redacted]	14.98	6.95	[redacted]
2		Manifestation-specific mortality rates adjusted based on the hanson et al. (2024) case series data	[redacted]	16.59	7.12	[redacted]
3		Reproduction of company scenario **2a** using EAG base case	[redacted]	18.99	7.92	[redacted]
4		Reproduction of company scenario **2b** using EAG base case	[redacted]	20.30	8.35	[redacted]
5		Reproduction of company scenario **2c** using EAG base case	[redacted]	17.43	7.48	[redacted]
6		Reproduction of company scenario **2a** using the adjusted manifestation-specific mortality rates based on the ESID data	[redacted]	15.66	6.89	[redacted]
7		Reproduction of company scenario **2b** using the adjusted manifestation-specific mortality rates based on the ESID data	[redacted]	18.60	7.72	[redacted]
8		Reproduction of company scenario **2c** using the adjusted manifestation-specific mortality	[redacted]	13.15	5.96	[redacted]

Scenario #	EAG base-case input	Alternative input	Incr. costs (£)	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Weighted ICER (£/QALY)
	HR (lymphoproliferation) = 0; HR(malignancy)=0.53 No treatment waning	rates based on the ESID data				
9		HR (lymphoproliferation) = 0.42; HR(malignancy)=0.55	[redacted]	17.15	7.44	[redacted]
10		10 % treatment waning effect at Year 5 after treatment	[redacted]	17.37	7.58	[redacted]
11		20 % treatment waning effect at Year 5 after treatment	[redacted]	16.74	7.37	[redacted]
Source: EAG outputs Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year						

Table 3: additional scenarios requested by NICE: sensitivity analysis for EAG's revised deterministic analysis (using 1.5% discount rate for both costs and health benefits)

Scenario #	EAG base-case input	Alternative input	Incr. costs (£)	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Unweighted ICER (£/QALY)	Weighted ICER (£/QALY)
	EAG base-case with 1.5% discount rate (deterministic)	N/A	[redacted]	18.01	12.06	[redacted]	[redacted]
	EAG base-case with 1.5% discount rate (probabilistic)	N/A	[redacted]	18.00	12.05	[redacted]	[redacted]
1	APDS-specific mortality rates based on the ESID data	Manifestation-specific mortality rates adjusted based on the ESID data	[redacted]	15.55	10.56	[redacted]	[redacted]
2		Manifestation-specific mortality rates adjusted based on the hanson	[redacted]	16.59	11.04	[redacted]	[redacted]

Scenario #	EAG base-case input	Alternative input	Incr. costs (£)	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Unweighted ICER (£/QALY)	Weighted ICER (£/QALY)
		et al. (2024) case series data					
3		Reproduction of company scenario **2a** using EAG base case	[redacted]	18.99	12.45	[redacted]	[redacted]
4		Reproduction of company scenario **2b** using EAG base case	[redacted]	20.30	13.24	[redacted]	[redacted]
5		Reproduction of company scenario **2c** using EAG base case	[redacted]	17.43	11.62	[redacted]	[redacted]
6		Reproduction of company scenario **2a** using the adjusted manifestation-specific mortality rates based on the ESID data	[redacted]	15.66	10.54	[redacted]	[redacted]
7		Reproduction of company scenario **2b** using the adjusted manifestation-specific mortality rates based on the ESID data	[redacted]	18.60	12.19	[redacted]	[redacted]
8		Reproduction of company scenario **2c** using the adjusted manifestation-specific mortality rates based on the ESID data	[redacted]	14.72	9.96	[redacted]	[redacted]

Scenario #	EAG base-case input	Alternative input	Incr. costs (£)	Incr. QALYs (undiscounted)	Incr. QALYs (discounted)	Unweighted ICER (£/QALY)	Weighted ICER (£/QALY)
9	HR (lymphoproliferation) = 0; HR(malignancy) =0.53	HR (lymphoproliferation) = 0.42; HR(malignancy) =0.55	[redacted]	17.15	11.49	[redacted]	[redacted]
10	No treatment waning	10 % treatment waning effect at Year 5 after treatment	[redacted]	17.37	11.67	[redacted]	[redacted]
11		20 % treatment waning effect at Year 5 after treatment	[redacted]	16.74	11.29	[redacted]	[redacted]

Source: EAG outputs
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year

EAG References

1. NICE. Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over. Highly specialised technologies guidance. National Institute for Health and Care Excellence (NICE); 2024. Available from: https://www.nice.org.uk/guidance/gid-hst10059/documents/draft-guidance [Accessed 1 Jan 2025].

2. Pharming Technologies BV. Leniolisib for activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over [ID6130]. Leniolisib Draft guidance stakeholder comments form. Highly specialised technology appraisal. Pharming Technologies BV; 2024.

3. Pharming Technologies BV. Leniolisib for activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over [ID6130] Document B. Company Evidence Submission. Highly specialised technology appraisal. Pharming Technologies BV; 2024.

4. Pharming Technologies BV. Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over [ID6130]. Cost-effectiveness model. Highly specialised technology appraisal. December 2024. Available from: [Accessed 10th July 2024].

5. Pharming Technologies BV. Leniolisib for activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over [ID6130]. Leniolisib Draft guidance stakeholder comments form – Appendix A.2: Expert Gathering Exercise. Highly specialised technology appraisal. Pharming Technologies BV; 2024.

[redacted]

7. Shillitoe, B. Activated phosphoinositide 3-kinase syndrome outcomes in the UK: An update from the UKPID registry. 2024. British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN) Conference; 10th December 2024.

8. Pharming Data on File. Natural History of Clinical Manifestations in Activated Phosphoinositide 3-Kinase δ Syndrome (APDS): Time-to-Event Analyses using the European Society for Immunodeficiencies-APDS Registry. [Manuscript In Development]. 2024.

9. *Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. Highly specialised technologies guidance.* National Institute for Health and Care Excellence (NICE); 2024. Available from: https://www.nice.org.uk/guidance/hst7/resources/strimvelis-for-treating-adenosine-deaminase-deficiencysevere-combined-immunodeficiency-pdf-1394905926085 [Accessed 1 Jan 2025].

10. Limaye, S; Menezes, S; Hu, H et al. Leniolisib reverses pulmonary dysfunction and immune deficiency in activated phosphoinositide 3-kinase delta syndrome 1 (APDS1) – TheraPID Study. 2023. ASCIA 2023 Conference; 5th September 2023.

11. Klemann, C; Baumann, U; Renz, DM et al. Complicated course of activated PI3Kδ syndrome-1 (APDS-1) ameliorated by leniolisib: a case study. 2023. International Primary Immunodeficiencies Congress.

12. Hanson, J; Bonnen, PE. Systematic review of mortality and survival rates for APDS. Clin Exp Med. 2024;24(1):17.

13. Trigg LA, Melendez-Torres GJ, Abdelsabour A, Lee D. Treatment Effect Waning Assumptions: A Review of National Institute of Health and Care Excellence Technology Appraisals. Value Health. 2024 Aug;27(8):1003-1011. doi: 10.1016/j.jval.2024.04.016. Epub 2024 Apr 26. PMID: 38679289.