Single Technology Appraisal

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

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Pharming Group N.V:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Main response
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3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Immunodeficiency UK:
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4. **Clinical Expert Statements**
   a. Great Ormond Street Hospital for Children Foundation NHS Trust - Austen Worth
   b. University College London – Siobhan Burns

5. **External Assessment Report** prepared by Newcastle TAR Group

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology appraisal

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

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
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Executive summary

B.1 Decision problem, description of the technology and clinical care pathway

- Activated phosphoinositide 3-kinase δ (PI3Kδ) syndrome (APDS) is an ultra-rare inborn error of immunity (IEI), estimated to affect 1–2 in 1,000,000 individuals. Unlike the majority of IEIs, APDS is characterised by a combination of both immune dysregulation and immune deficiency;[1-7] APDS is therefore one of the more severe IEIs.
- APDS arises as a result of pathogenic variants in genes encoding subunits of the PI3Kδ enzyme complex. Hyperactivity of the enzyme causes excessive signalling in the PI3Kδ pathway, leading to the abnormal development and maturation of immune cells, such as B and T cells.[8, 9]
- The presence of dysfunctional immune cells leads to individuals with APDS experiencing severe, progressive and potentially life-threatening multi-system manifestations,[3, 4, 10, 11] with damage accumulating over time (e.g. damage within the lung leading to bronchiectasis-associated airway disease).[3, 10, 12-14] As such, APDS can lead to early mortality (with lymphoma a dominant cause of mortality), as well as a high risk of developing malignancy early in life and irreversible end-organ damage, such as advanced lung disease and hearing loss.[7, 12, 15, 16] Other common manifestations include lymphoproliferation, autoimmune cytopenias, inflammatory bowel disease and/or enteropathy, as well as recurrent and often severe oto-sinopulmonary infections.[3, 10, 13, 17]
- APDS is associated with a significant shortening of life, with one in four adults not surviving into early adulthood.[15, 18-20] People with APDS experience multiple heterogenous manifestations simultaneously, accumulating over time, which can severely impair patient HRQoL and daily activities.[11, 21-25]
- Individuals with APDS describe feeling exhausted and drained, both mentally and physically, feeling isolated, having “no plans for the future”, and feeling anxious regarding the risk of developing lymphoma and “not making it far”. Living with APDS also has a broader impact on the wellbeing of families, friends and carers.[11, 23, 26]
- There are currently no licensed treatments available for APDS in the UK. Current clinical management in the UK is limited to supportive care, including but not limited to IRT, antimicrobial treatment and multiple lines of immunosuppressive therapies; complex polypharmacy approaches are required to manage the multiple manifestations associated with immune dysregulation and/or immune deficiency.[3, 13, 14, 17, 18, 27, 28] Individuals experience intensive treatment regimens, with frequent and prolonged hospital visits with invasive treatments.[3, 13, 15, 29-31]
- Haematopoietic stem cell transplant (HSCT) is the only potentially curative treatment option for some individuals with APDS when clinically indicated, although it is associated with significant treatment-related morbidity and mortality risks, with some people requiring multiple transplants.[12, 32]
- Leniolisib is the first targeted therapy for APDS that selectively inhibits p110δ, resulting in the normalisation of the PI3Kδ pathway. This targeted mechanism of action allows leniolisib to treat the underlying cause of APDS, improving both the immune dysregulation (e.g. lymphoproliferation) and immune deficiency (e.g. severe, recurrent and/or persistent infections) observed.[9, 17, 27, 33-35] In turn, this leads to improvements in

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HRQoL, improving an individual's energy levels and ability to complete daily activities, as well restoring their hope and general wellbeing.[17, 26, 35-37]

B.2 Clinical effectiveness

- The efficacy and safety of leniolisib for the treatment of individuals with APDS has been explored comprehensively in three international clinical trials: Study 2201 Part II (placebo-controlled, triple-blinded RCT), Study 2201E1 (long-term extension) and Study 2201 Part I (dose-escalation). These trials enrolled adults and adolescents 12 years of age and older, in line with the population defined within the final scope for this evaluation.[17, 27, 35, 38]

Efficacy and Safety

- By targeting the underlying cause of APDS, treatment with leniolisib results in improvements in immunophenotype:
  - Leniolisib met the co-primary endpoint in Study 2201 Part II, producing a statistically significant increase in naïve B cells as a percentage of total B cells relative to placebo by Week 12 (p=0.0002), which was maintained throughout Study 2201E1, indicating normalisation in B cell development and maturation.[17, 35, 39]
- Leniolisib is associated with significant improvements in the immune dysregulation associated with APDS:
  - The other co-primary endpoint in Study 2201 Part II was also met, with leniolisib demonstrating statistically significant improvements in log10 transformed sum of product diameters (SPD) of index lesion size versus placebo (nodal p=0.0006). Reductions in lymphoproliferation were maintained in Study 2201E1, demonstrating sustained decreases in the incidence of swollen lymph nodes across the body.[17, 35]
  - Secondary and exploratory endpoints in Study 2201 Part II also demonstrated statistically significant reductions in spleen bi-dimensional size (p=0.0148) and spleen organ volume (p=0.002) compared to placebo.[17]
  - Findings from Study 2201 and Study 2201E1 demonstrate that leniolisib treatment is associated with numerical improvements in cytopenia cases, suggesting a reduction in autoimmunity.[17, 35, 38]
  - Leniolisib treatment also led to improvements in two out of three participants in the clinical trials who experienced gastrointestinal manifestations who were investigated as part of a case study; 2/2 participants remain symptom-free and have discontinued use of other treatments for their gastrointestinal manifestations.[40]
- Leniolisib improves the immune deficiency associated with APDS, as demonstrated by a reduced rate of infections and treatments, as well as cessation of IRT with long-term leniolisib treatment:
  - In Study 2201E1, a nominally significant decrease in annualised infection rates of 25% was reported with each additional year of leniolisib treatment (−0.282 infections per year, one-sided p=0.0256; DCO: 13th March 2023).[41]
  - Reductions in the incidence of infections were accompanied by sustained reductions in IRT use, and no increase in antibiotic usage, throughout Study 2201E1.[35] Furthermore, during the OLE, 10/27 participants had reduced IRT usage, or achieved and maintained IRT freedom (538–1398 days of IRT freedom at last study visit; DCO: 13th March 2023). [17, 35, 38, 41, 42]
- In a case study of six study participants, of the three participants who had developed bronchiectasis prior to entering Study 2201 Part I, bronchiectasis did not progress in

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any of the individuals through six years of treatment with leniolisib during Study 2201E1, no additional pulmonary support was required, and all three individuals were stable at Year 6 of treatment.[36]

- In Study 2201E1, as of the latest DCO (13th March 2023), a case of classical Hodgkin's lymphoma was reported which led to treatment discontinuation; this AE was not considered to be related to leniolisib, by the investigator. No other new malignancies were reported in the clinical trials, including in participants with a history of lymphoma[35] and no participants received HSCT whilst receiving leniolisib treatment.[43]
- The clinical improvements seen with leniolisib treatment have a positive impact on the everyday lives of people with APDS, with clinically meaningful improvements observed in physical functioning and general health SF-36 scales, through to Week 208 of the study.[37, 38, 44]
- Leniolisib was generally well tolerated by all participants in Study 2201 Part I and Part II, with an overall AE profile comparable to placebo; leniolisib remained generally well tolerated with long-term therapy during Study 2201E1. In Study 2201 and Study 2201E1, none of the AEs/TEAEs reported that led to discontinuation or death were determined to be study drug related.[17, 27, 35, 38]

B.3 Cost effectiveness

- A de novo health state transition model was developed to evaluate the cost-effectiveness of leniolisib versus current clinical management in adults or adolescents with APDS aged 12 years or older, in line with the final scope from NICE for this evaluation.
- The results of the base case cost-effectiveness analysis demonstrate that leniolisib (with proposed PAS) is associated with increased health benefits versus current clinical management over a lifetime horizon, and was found to be plausibly cost-effective compared with current clinical management at a willingness-to-pay threshold of £100,000/QALY, yielding an ICER of £[redacted]/QALY. Results of scenario analyses showed that the base case ICER was robust to various data sources and assumptions around model inputs. Additionally, in the probabilistic sensitivity analysis (PSA), leniolisib had a [redacted]% chance of remaining cost-effective at a willingness to pay threshold of £100,000 weighted QALY gained.

Conclusion

Leniolisib is the first disease modifying therapy for people with APDS. Results from the clinical trial programme demonstrate that leniolisib improves outcomes for people with APDS across a range of clinically- and patient-relevant endpoints, whilst being generally well tolerated. Leniolisib targets the underlying pathophysiology of APDS, normalising immune cell subset levels. Improved immune system functioning translates into long-term improvements and reductions in the incidence and/or severity of manifestations, leading to a reduction and cessation in the use of supportive medications, as well as improvements in patient HRQoL. The results of the base case cost-effectiveness analysis demonstrate that leniolisib (with proposed PAS) is associated with increased health benefits versus current clinical management over a lifetime horizon, and was found to be plausibly cost-effective compared with current clinical management.

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission demonstrates the clinical and cost effectiveness of leniolisib within its full, proposed marketing authorisation for activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adults and adolescents 12 years of age and older (Table 1).[45]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with APDS 12 years of age and older	Adults and adolescents with APDS 12 years of age and older [redacted].	This population differs to that specified in the pre-invitation scope [redacted]. The population is in line with the: • participant eligibility criteria for the pivotal leniolisib trials • the anticipated licence wording from the Medicines and Healthcare products Regulatory Agency (MHRA), and • the population anticipated to receive leniolisib in UK clinical practice
Intervention	Leniolisib	Leniolisib	N/A – decision problem is aligned with final scope

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Comparator(s)	Established clinical management without leniolisib	Established clinical management without leniolisib, specifically covering: antimicrobials, immunoglobulin replacement therapy (IRT), immunosuppressive therapies (including steroids, rituximab and mammalian target of rapamycin [mTOR] inhibitors), haematopoietic stem cell transplantation (HSCT), surgery and other procedures, in line with current practice in the UK.	N/A – decision problem is aligned with final scope
Outcomes	• Infections • Lung function • Fatigue • Mortality • Disease severity • Immunophenotype measures (lymphocyte counts, immunoglobulin levels, cytokine and chemokine levels) • Immune system function (lymph node size, spleen and liver volume size, use of IRT) • Adverse and serious effects of treatment • Health-related quality of life (HRQoL)	• Immunophenotype measures (including lymphocyte counts [such as naïve B cells], serum immunoglobulin levels, and cytokine and chemokine levels) • Immune dysregulation measures (including lymphoproliferation, lymphadenopathy [lymph node size], splenomegaly [spleen volume/size], cytopenias and gastrointestinal manifestations) • Immune deficiency measures (infections, use of IRT and antibiotics, and hearing loss) • Lung disease (bronchiectasis-associated airway disease and advanced lung disease) • Fatigue • Malignancy and mortality • Disease severity and HRQoL (SF-36 and PtGA) • Adverse and serious effects of treatment	All outcomes requested by NICE in the final scope are presented in the evidence submission. Neither lung disease nor mortality were investigated as pre-specified efficacy outcomes in the clinical trial programme for leniolisib. However, safety data are available from the clinical trials for both outcomes, including reports of respiratory disorders, infective exacerbations of bronchiectasis, and deaths.[17, 46] In addition, real-world evidence is available for the impact of leniolisib on lung disease.[47, 48] This evidence submission addresses lung disease and mortality in Section B.2.6.4 and Section B.2.6.6, respectively.

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Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	N/A	Leniolisib treatment is associated with a number of benefits which are not captured in the QALY calculation and hence, the benefit of leniolisib may be underestimated: • Treatment with leniolisib may result in clinical benefits in non-immune cells however,[49-51] these manifestations are not included in the model based on lack of available evidence. • Individuals with APDS treated with leniolisib may experience improved productivity, and increased working hours at work/school (captured by the WPAI-CIQ questionnaire), which may have a wider societal benefit.[37, 38] • Leniolisib treatment reduces the need for IRT in individuals with APDS, diminishing the burden of IRT on patients and the NHS,[52] supporting supply chain easing,[53] and reducing the risk of the transfer of new infections and disease from this blood-derived product.[54] The burden of IRT continues to be a significant subject of discussion in the UK.[55] • Leniolisib reduces the need for antibiotics, and in turn, the incidence of individuals who present with antimicrobial-resistant infections is expected to concordantly decrease, alongside the associated high costs and burden.[56-58] • Treatment with leniolisib leads to the improvement of manifestations associated with APDS and therefore, can positively impact caregiver HRQoL.[37] • In line with the UK Rare Disease Strategy,[59] leniolisib would provide an effective treatment	N/A

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		option, promoting equitable access across the licensed APDS population in the UK.	
Special considerations including issues related to equity or equality	N/A	N/A	There are currently no licensed treatments available for APDS in the UK. This may lead to sub-optimal and inconsistent use of off-label medicines and variable polypharmacy approaches in the management of APDS.[3, 6, 27, 28] Additionally, individuals of African descent are often faced with inequalities in access to HSCT, due to having the lowest probability of finding an appropriately matched unrelated donor.[60] Access to HSCT may also be restricted for some young people with APDS due to the lack of parental consent.[61]

Abbreviations: APDS: activated PI3K delta syndrome, HSCT: haematopoietic stem cell transplantation, HRQoL: health-related quality of life, IRT: immunoglobulin replacement therapy, MHRA: Medicines and Healthcare products Regulatory Agency; mTOR: mammalian target of rapamycin, NICE: National Institute of Health and Care Excellence; PtGA: patient global assessment; SF-36: short-form 36; UK: United Kingdom.
Source: Ayuk et al., 2019,[60] Bartok et al., 2012,[50] Coulter et al., 2018,[3] Dagostar et al., 2019,[56] Department of Health and Social Care, 2022,[59] Fujita et al., 2020,[51] Her Majesty's Government,[57] Limaye et al., 2023,[48] Maccari et al., 2018,[6] Magaria et al., 2022,[49] National Health Service, 2019,[53] National Health Service, 2024,[55] NHS England,[58] Patel et al., 2014,[52] Pharming Data on File, 2020,[37] Pharming Data on File, 2023,[47] Pharming Data on File, 2023,[38] Rao et al., 2017,[27] and Singh et al., 2020.[28]

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B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	**Approved name**: Leniolisib **Brand name**: Joenja®
Mechanism of action	APDS is caused by hyperactivity of the PI3Kδ enzyme complex. Leniolisib is an oral, selective, small-molecule inhibitor of p110δ,[17] the catalytic subunit of the PI3Kδ enzyme complex.[9, 62, 63] Leniolisib selectively inhibits p110δ, resulting in normalisation of the PI3Kδ pathway by inhibiting the recruitment and activation of a range of downstream messengers in the PI3Kδ signalling pathway.[27, 45] In turn, this diminishes the dysregulation of immune B and T cells and re-establishes their normal development and maturation.[17, 45] In this way, leniolisib improves both the immune dysregulation and immune deficiency observed in APDS.[17]
Marketing authorisation/CE mark status	A marketing authorisation application has been submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of APDS in adults and adolescents 12 years of age and older, [redacted], following the International Recognition Procedure. Approval from the MHRA is expected by [redacted]. Pharming will update NICE should these expected timelines change. Pharming have established a global Early Access Programme (EAP), with 72 individuals with APDS having received leniolisib, including six in the UK across three centres.[64] Applications from a further four UK centres are also being processed.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Leniolisib (Joenja®) is anticipated to be indicated for the treatment of APDS in adults and adolescents 12 years of age and older [redacted].[45]
Method of administration and dosage	Leniolisib is an oral film-coated tablet.[45] The recommended dose in adult and adolescent individuals with APDS who weigh more than 45 kg is 70 mg leniolisib twice daily, approximately 12 hours apart.[45] Full details of the dosing for leniolisib in people with APDS can be found in the draft SmPC, provided in the submission reference pack.[45]
Additional tests or investigations	Genetic tests are available for APDS and are part of standard practice for the management of suspected IEIs in the NHS. No additional monitoring or testing, beyond what is already conducted for individuals with APDS, is anticipated to be required for treatment with leniolisib.
List price and average cost of a course of treatment	The anticipated list price of leniolisib is [redacted], excluding VAT.
Patient access scheme (if applicable)	A confidential PAS discount of [redacted] has been submitted to the NICE PAS Liaison Unit (PASLU), resulting in a discounted price [redacted].

Abbreviations: APDS: activated PI3K delta syndrome; IEI: inborn error of immunity; MHRA: Medicines and Healthcare Regulatory Agency; NICE: National Institute for Health and Care Excellence; PI3Kδ: phosphoinositide 3-kinase δ; PAS: patient access scheme; PID: primary immunodeficiency disorder; SmPC: summary of product characteristics; VAT: value added tax.

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Source: Fruman et al., 2017,[9] Jean et al., 2014,[63] Lucas et al., 2016,[62] Pharming et al., 2024,[45] Rao et al, 2017,[27] Rao et al., 2023.[17]

B.1.3 Expert Consultancy and natural history studies

Natural history studies

Considering that APDS is an ultra-rare IEI that was only recently described, various analyses were conducted to investigate the characteristics of people with APDS in the European Society for Immunodeficiencies (ESID) registry. The registry is a prospective, observational, international registry of patients of all ages with primary immunodeficiencies (PIDs) and the UKPID registry is a major contributor. The registry includes a cohort of individuals with a genetic confirmation of APDS,[6, 13, 43, 65, 66] and is the largest registry for people with PIDs worldwide.[65] Findings from these analyses have been presented throughout Section B.1 to supplement literature regarding the natural history of APDS and the clinical care pathway. Furthermore, data from the ESID registry was used in an externally controlled indirect matched comparison, presented in Section B.2.6.1, and as a key data source to inform inputs for the current clinical management arm of the economic model (see Section B.3). For further information on the ESID registry analyses, please refer to the summary report provided in the reference pack.[16]

Expert Consultancy project

The Expert Consultancy project aimed to gather expert insights to inform this submission and accompanying de novo health economic model. The project comprised of three distinct exercises, which address the various areas of uncertainty within the evidence base for APDS, and which validate key assumptions within the model and submission.[14]

- **Exercise 1** used **modified structured expert elicitation** (SEE) with the aim of generating estimates of the long-term impact of leniolisib on APDS manifestations and mortality[14]
- **Exercise 2** consisted of an **EQ-5D-5L survey** – please refer to the full report for details of this exercise[23]
- **Exercises 3 and 4** were **Qualitative and Quantitative Surveys** respectively, that aimed to generate and validate key assumptions informing this evidence submission and the cost-effectiveness model for leniolisib[14]

Ten clinical experts with expertise in APDS from the UK, Europe and Canada were recruited and were distributed in various groups to participate in the exercises, as shown in Table 3. English clinical experts participated in all four exercises.[14]

Table 3. Number of participating clinical experts in the Expert Consultancy project exercises 1 and 3–4

Exercise number and type of exercise	Number of participating clinical experts	Countries of origin for the participating clinical experts
Exercise 1 – Modified SEE	5 – *with prior experience of treating people with leniolisib*	England, Wales, Italy, Spain and Canada
Exercise 3 – Qualitative survey	5	England and Italy
Exercise 4 – Quantitative survey		

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Considering the rarity and recent recognition of APDS,[1, 2] and the scarcity of published evidence in APDS, findings from the exercises in the Expert Consultancy project provide robust and valuable evidence to inform this submission, supporting the conclusions drawn from the leniolisib clinical trials (see Section B.2) and informing key inputs for the economic model (see Section B.3).[14]

Exercise 1

The modified SEE was carried out in line with best practices;[67-69] clinical experts were provided with training slides and an Evidence Dossier of relevant data to review before completing the exercise. Exercise 1 was divided into two parts:[14]

- Clinical experts first completed the Part 1 survey, which aimed to elicit estimates on the occurrence of APDS manifestations and mortality in people with APDS treated with current clinical management. Kaplan-Meier (KM) data for manifestation and mortality occurrence with current clinical management were presented, sourced from the cohort of individuals with APDS in the ESID registry and Hanson and Bonnen, 2024,[19] respectively.
    - Questions included estimating upper and lower plausible limits of manifestation occurrence and mortality, as well as choosing the most clinically plausible parametric curves to represent manifestation occurrence and mortality over time.
- In the Part 2 survey, clinical experts were presented with ESID KM point estimates and/or the aggregated results from Part 1, and asked to estimate the impact of leniolisib on the occurrence of the manifestations and survival.
    - In order to elicit treatment effect estimates relevant to the age range anticipated to be licensed for leniolisib (age 12 onwards), inverted ESID Kaplan-Meier data and the Part 1 results were adjusted to start from age 12 onwards, rather than age 0.
    - Clinical experts then responded with their estimates of upper and lower plausible limits for APDS manifestation incidence and proportions of individuals experiencing improvements of manifestations, in addition to survival, in people with APDS receiving leniolisib.

Results from Part 1 and Part 2 were used to calculate hazard ratios (HRs) representing the estimated likelihood of incidence of manifestations and survival in people with APDS receiving leniolisib, in comparison to current clinical management.[14]

Exercise 3 and 4

In the Qualitative Expert Elicitation survey, questions required a “yes” or “no” answer, or a five-point Likert scale response. In the Quantitative Expert Elicitation survey numerical responses were requested.[14]

For each question across Exercises 1, 3 and 4, clinical experts had the opportunity to register if they were particularly unsure, or lacked the relevant experience or expertise to answer. Sensitivity analyses were conducted where these responses were excluded from the combined results. Follow-up calls were conducted with clinical experts after the completion of each exercise to enable validation of the results received, and clarification of certain responses.[14]

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B.1.4 Health condition and position of the technology in the treatment pathway

B.1.4.1 Introduction to APDS

Summary

- APDS arises as a result of pathogenic variants in genes encoding subunits of the phosphoinositide 3-kinase delta (PI3Kδ) enzyme complex.[8, 9]
- PI3Kδ enzyme complexes are formed of a p85α regulatory subunit and p110δ catalytic subunit. APDS1 is caused by gain-of-function variants in the *PIK3CD* gene, which encodes p110δ, while APDS2 is caused by loss-of-function variants in *PIK3R1*, which encodes p85α; both variants result in hyperactivation of the PI3Kδ enzyme complex.[70]
- Resultant hyperactivity of the PI3Kδ signalling pathway has multiple detrimental consequences, including the abnormal development and maturation of immune cells. The presence of dysfunctional immune cells leads to individuals with APDS experiencing severe, progressive and potentially life-threatening multi-system manifestations (see Section B.1.4.2).[3, 4, 10, 11]
- Unlike the majority of inborn errors of immunity (IEI), APDS is characterised by a combination of both immune dysregulation (with manifestations such as lymphoproliferation, splenomegaly, enteropathy, lymphoid hyperplasia and autoimmunity) and immune deficiency (which can lead to severe, recurrent and/or persistent infections), with damage accumulating over time (e.g. damage within the lung leading to bronchiectasis-associated airway disease and advanced lung disease);[3, 10, 12-14] APDS is therefore one of the more severe IEIs.
- Despite current treatments, APDS is a progressive disease that can lead to early mortality (with lymphoma a dominant cause of mortality), as well as irreversible end-organ damage, such as advanced lung disease and/or hearing loss.[7, 12, 15, 16]

APDS as an IEI

Inborn errors of immunity (IEIs), also known as primary immunodeficiency disorders (PIDs), are a group of conditions caused by pathogenic gene variants, that result in changes in expression or function of proteins that are necessary for immune system functioning.[8, 71, 72] APDS is an ultra-rare IEI that was only recently described in 2013.[2] APDS is considered to be one of the combined "immunodeficiencies affecting both antibody-mediated and cellular immunity" (i.e. affecting B cells and antibodies, as well as T cells; see 'Disease pathophysiology'),[71] making it one of the more severe IEIs. The combination of immune dysregulation and immune deficiency in APDS leads to severe impacts on the quality of life (QoL) of people with APDS.[3, 4, 10, 11]

Disease pathophysiology

Hyperactivity of the PI3Kδ signalling pathway

The PI3Kδ pathway is a key signalling pathway that consists of complex interactions. Activity of the pathway must be dynamically regulated to ensure appropriate control of a wide range of cellular processes, including proliferation, survival, differentiation, maturation and metabolism.[9] In

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healthy individuals without APDS, activity in the PI3Kδ pathway is balanced, with associated pathways and processes being activated or inhibited.[28, 73-75] A key component regulating activity of the PI3Kδ pathway is the PI3Kδ enzyme complex, which is mainly expressed in immune cells (white blood cells or leukocytes),[33, 62] although expression and activity the PI3Kδ enzyme complex has also been reported in non-immune cells.[49-51]

APDS arises as a result of pathogenic variants in the gene encoding the PI3Kδ enzyme complex,[76] which can either be inherited from parent(s) or occur de novo.[28, 70, 75] PI3Kδ enzyme complexes are formed of a p85α regulatory subunit and p110δ catalytic subunit.[9, 63] Gain-of-function variants in the *PIK3CD* gene (which encodes the catalytic subunit p110δ) are termed APDS1, whilst loss-of-function variants in the *PIK3R1* gene (which encodes the regulatory subunit p85α) are termed APDS2.[28, 76] Both APDS-associated pathogenic gene variants cause hyperactive signalling in the entire PI3Kδ pathway, which in turn leads to abnormal development and maturation of immune cells, as next discussed. The presence of dysfunctional immune cells leads to severe, progressive and potentially life-threatening multi-system manifestations (see Section B.1.4.2).[7, 12, 13, 15, 29, 77]

PI3Kδ in the immune system

Adaptive immunity is mainly delivered by B and T cells (also known as B and T lymphocytes).[9, 78] Hyperactive PI3Kδ signalling in APDS has detrimental effects on the development and maturation of B and T cells, impairing their functioning.[75]

Impact of hyperactive PI3Kδ signalling on B cells

Antigens are 'non-self' (foreign) substances which induce an immune response, and are typically present on pathogens or abnormal cells (such as cancerous cells).[79] B cells are the category of immune cell that produce antigen-specific antibodies (also known as immunoglobulins [Ig]), as a defence against these 'non-self' substances.[80]

Transitional B cells are immature B cells that undergo maturation to become naïve B cells in the lymphatic tissues (such as the spleen or lymph nodes).[80] Naïve B cells, upon interacting with antigens,[81] become mature B cells, which are pivotal for the production of antibodies that specifically bind to the antigen.[80, 82] Initially, antibodies of the IgM class are produced by mature B cells before immunoglobulin class switching subsequently occurs to express other classes of antibodies (IgG, IgE or IgA).[80, 82] Ultimately, mature B cells will form short-lived plasmablasts (which produce large quantities of antibodies) or long-lived memory B cells. These memory B cells can transform into long-lived plasma cells, and can provide an accelerated response upon re-encountering the same antigen, by either producing many antibodies or further memory B cells.[80, 82-84]

Hyperactive PI3Kδ signalling in people with APDS leads to the arrested development of B cells,[76] negatively impacting the maturation of B cells, which in turn, impedes an effective antibody-based immune response. Lymphocytes from individuals with APDS show:

- Elevated levels of early-stage, undifferentiated B cells (transitional B cells)[12, 75, 76]
- A lower-than-normal proportion of naïve B cells[12, 75, 76]
- Fewer switched memory B cells, indicating that immunoglobulin class switching in people with APDS is impaired[9, 29, 75, 85]

Impaired class switching limits B cells to produce low affinity IgM rather than switching to produce higher affinity IgG, IgA and IgE,[9, 62, 85] leading to dysgammaglobulinemia (deficiency of

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one or more, but not all classes of immunoglobulins).[86] This leads to a deficit in the antibody classes required to fight infections, decreasing the effectiveness of the adaptive immune response and leading to poor vaccine responses.[3, 12, 18, 77, 87] Alongside antibody deficiency, the disruption to B cell development in APDS contributes to manifestations associated with immune dysregulation, including:

- Increased susceptibility to persistent, severe, or recurrent viral infections (such as herpesviruses: Epstein-Barr virus [EBV] and cytomegalovirus [CMV]; see Figure 1)[12, 88]
- Excessive proliferation of immune cells (lymphoproliferation; see Section on 'Lymphoproliferation (lymphadenopathy)')[3, 75]
- Impaired ability to suppress 'self'-reactive B cells which attack the body's own healthy cells and tissues, increasing susceptibility to autoimmunity (triggering of an unnecessary immune response)[89, 90]

Increased risk of malignancy (see 'Malignancy, including lymphoma

- ') as B cells are known to have anti-cancer activities[87, 91]

Impact of hyperactive PI3Kδ signalling on T cells

T cells are the category of immune cell that activate a cell-mediated response (an immune response not reliant on the production of antibodies), as a defence against antigens and 'non-self' cancerous cells.[79, 92] There are various T cell subsets which are important in helping the B cell response described above. There are three main subsets of T cells: cytotoxic T cells (CD8+), helper T cells (CD4+) and regulatory T cells (Treg; CD4+).[93]

The T cell response is initiated when a mature naïve T cell (of any subset) encounters an antigen, developing into either an effector T cell (short-lived and responsible for the short-term immune response) or a memory T cell (has been previously been activated by an antigen and maintains long-term T-cell mediated immunity).[94, 95] Ultimately, T cells may lose their ability to participate in the immune response and become exhausted;[96] the programmed cell death protein 1 (PD-1) is often used as a marker for T cell exhaustion.[97]

In people with APDS, hyperactivity of the PI3Kδ pathway leads to:

- An increase in short-lived effector T cells, at the expense of naïve and memory T cells, promoting inflammation[98, 99]
- An inverted CD4+/CD8+ T cell ratio, with lower proportions of CD4+ cells and increased proportions of CD8+ cells.[3, 98, 100] A low or inverted CD4+/CD8+ T cell ratio is associated with immune dysregulation, immune senescence (deterioration of the immune system with age) and chronic inflammation[101]
- An increase in senescent and exhausted effector T cells due to the terminal differentiation of CD8+ T cells[29, 75, 98]

The functional impairment of T cells in people with APDS has three main consequences:

- A reduced ability to respond to infections[12, 13, 18]
- Impaired ability to recognise the body's own healthy cells and tissues as 'self', which increases susceptibility to autoimmunity[102-104]
- Weakened tumour surveillance against 'non-self' cancerous cells[92]

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Summary

Overall, the functional impairment of both B and T cells in people with APDS leads to individuals experiencing severe, progressive, and potentially life-threatening multi-system manifestations. The combination of immune dysregulation and immune deficiency of APDS can severely impair patient QoL. The following section explores the clinical manifestations of APDS and their subsequent impact on patient HRQoL (Section B.1.4.2).

B.1.4.2 Impact of APDS

Summary

Manifestations

- The combination of immune dysregulation and immune deficiency in APDS leads to severe and potentially life-threatening multi-system manifestations. Common manifestations include malignancy (with an increased risk of lymphoma early in life), bronchiectasis-associated airway disease, advanced lung disease, lymphoproliferation, autoimmunity, inflammatory bowel disease and/or enteropathy, as well as severe, recurrent and/or persistent infections.[3, 10, 13, 17, 18, 105]
- APDS is a progressive disease with an early age of onset; individuals with APDS experience an increase in both the frequency and range of manifestations over time.[10, 13, 18, 106] Individuals with APDS will also experience multiple, heterogenous manifestations across distinct organ systems,[16] which can lead to irreversible end-organ damage such as advanced lung disease and/or hearing loss,[12-14] all of which has a substantial impact on patient HRQoL and life expectancy.[4, 11, 23]

Life Expectancy

- APDS is associated with a significant shortening of life, with one in four adults not surviving into early adulthood.[15, 18-20] Survival analyses have reported a survival of 68% at age 40.[19] In the ESID registry, 50% of individuals experienced either malignancy or death by age 40, rising to 73% by age 57, the latest age at which data is available.[16] However, due to the ultra-rare status of APDS and likelihood some individuals did not historically receive a specific diagnosis of APDS, mortality is likely underreported.[43]
- Accumulation of severe manifestations, increased risk of malignancy, and the adverse effects of current treatments all contribute to early mortality in APDS.[7, 12, 15, 19] Lymphoma is the dominant cause of mortality, resulting in 24–42% of all fatalities seen in APDS (the median age of malignancy diagnosis is 19 years).[10, 13, 19, 107] Non-malignant causes of early mortality in APDS have been reported to include severe respiratory infections, bronchiectasis, respiratory failure, cardiopulmonary arrest, bowel perforation, septic shock, multiple organ failure following HSCT and pulmonary haemorrhage.[3, 12, 13, 18, 107]

Impact on HRQoL

- Individuals with APDS experience feelings of loneliness, isolation, and exhaustion,[11, 21, 22] often accompanied by a sense of hopelessness for the future.[11, 23, 26] They also require frequent hospital visits with invasive treatments for the management of different manifestations.[3, 13, 15, 29-31] Living with APDS therefore has broad and substantial impacts on individuals leading to anxiety, depression and stress,[11, 23, 108, 109] as well as affecting their ability to perform daily activities, work and/or participate in education.[14]

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- People with APDS experience multiple heterogenous manifestations simultaneously, which lead to cumulative negative impacts on HRQoL.[7, 13, 110] The increased risk of malignancy with APDS from early in life,[3, 13, 18, 105] and irreversible end-organ damage such as advanced lung disease and/or hearing loss, have notable impacts on patient HRQoL.[4, 10, 14, 17]
    - Considering lymphoma, individuals can experience significant psychological distress due to constant anxiety about the occurrence/recurrence of lymphoma, fear of poor response to treatment, social isolation, panic, suffering and death;[23, 111] in addition to the physical symptoms of lymphoma, such as fatigue, pain and night sweats.[112]
    - Individuals with APDS report that lung disease can cause individuals with APDS to struggle with their breathing, experience chest pain and need supplementary pulmonary support. Lung disease can also lead to sleep apnoea, negatively impact energy levels and lead to feelings of frustration.[11, 23, 47, 48, 64, 113]Moreover, individuals with APDS and lung disease report feeling anxiety about the irreversible end-organ damage and scarring they have experienced.[11, 23] In severe cases, advanced lung disease can progress and lead to death from respiratory failure in its end stages.[12, 19]

Epidemiology

- APDS is an ultra-rare condition, with recent literature reporting that APDS affects between 1–2 per 1,000,000 individuals globally.[4] Based on UKPID data and medical team insights, there are currently an estimated [redacted] individuals with APDS in England, of which [redacted] are believed to be aged 12 years and older.

Disease course and mortality

Disease course

The combination of immune dysregulation and immune deficiency in APDS leads to severe, progressive and potentially life-threatening multi-system manifestations, as shown in Figure 1.[3, 4, 10, 11] Two recent analyses of the ESID registry by Thalhammer et al., 2021 and Maccari et al., 2023 found that 36% of the APDS cohort presented with manifestations in the first year of life, >70% by age 5, and >90% in between the ages of 6–10 (n=122; March 2019 dataset), and the median age at first clinical manifestation was 1 year (n=170, November 2022 dataset), respectively.[13, 114]

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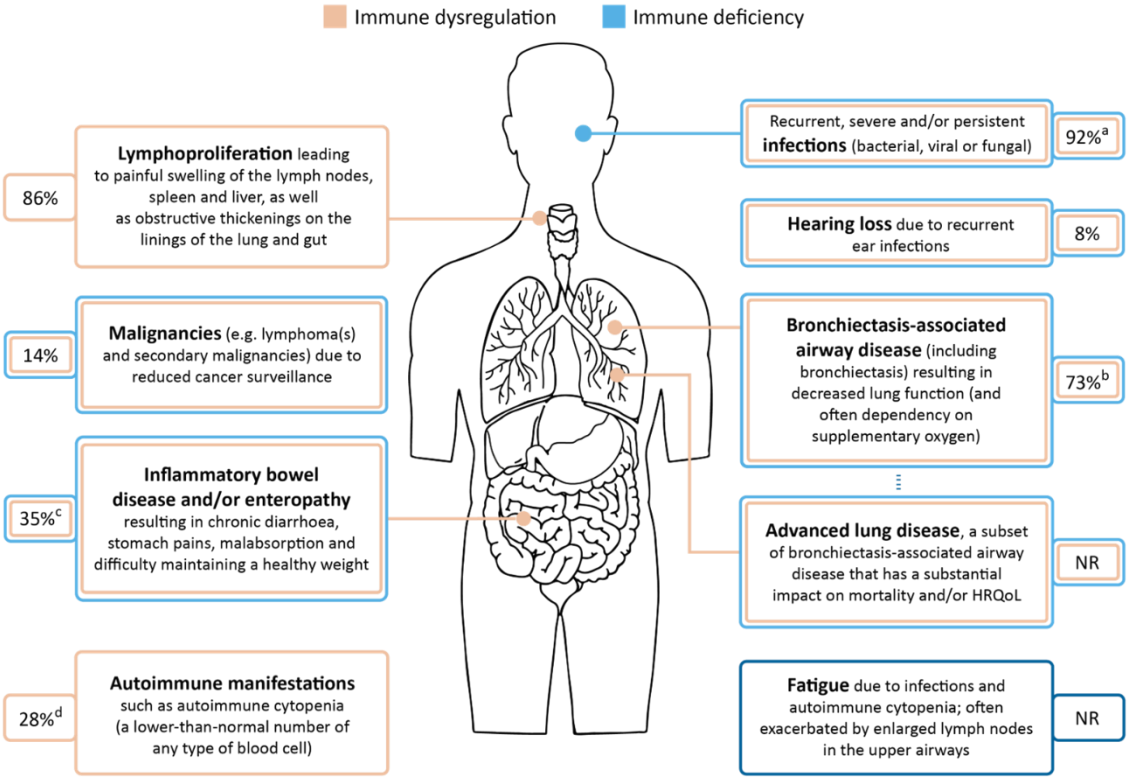
Figure 1. Clinical manifestations commonly seen in people with APDS, including percentage of individuals experiencing each manifestation



Footnote: [a,b,c]The percentage of individuals experiencing respiratory infections, chronic lung disease and inflammatory bowel disease in the Maccari et al., 2023 cohort, respectively. Furthermore, in the Maccari et al., 2023 cohort, it was reported that 50% of individuals with APDS were experiencing bronchiectasis.[13]
Abbreviations: APDS: APDS: Activated PI3Kδ syndrome; HRQoL: health-related quality of life.
Source: Büsch et al., 2023,[107] Coulter et al., 2017,[12] Coulter et al., 2018,[3] Jamee et al., 2019,[18] Maccari et al., 2023,[13] Pharming Data on File,[43] Pharming Data on File, 2023,[115] Rao et al., 2023.[36]

Respiratory infections are often first to occur, early in life, and are recurrent (with almost all individuals affected by the age of 15 years).[6, 12] Recurrent and often severe oto-sinopulmonary infections can lead to irreversible end-organ damage, such as advanced lung disease and/or permanent hearing loss.[6, 12-14, 24] In later childhood, individuals may develop autoimmune and autoinflammatory conditions, such as cytopenias (including anaemia), thrombocytopenic purpura, colitis, and glomerulonephritis.[24, 116] In late adolescence people with APDS may develop malignancy; by the age of 20 years, 17% of individuals with APDS within the ESID registry had experienced a type of malignancy, and 43% by the age of 40 years (November 2023 dataset).[16] Moreover, in a cohort study of individuals with APDS2, it was estimated that there is a 78% cumulative risk for lymphoid malignancy at 40 years of age.[15]

Recent analyses of the ESID registry shows that the median age for individuals with APDS experiencing three manifestations was seven, with six manifestations experienced by age 33 (Figure 2). By adolescence the majority of individuals with APDS will experience multiple life-limiting manifestations.[16]

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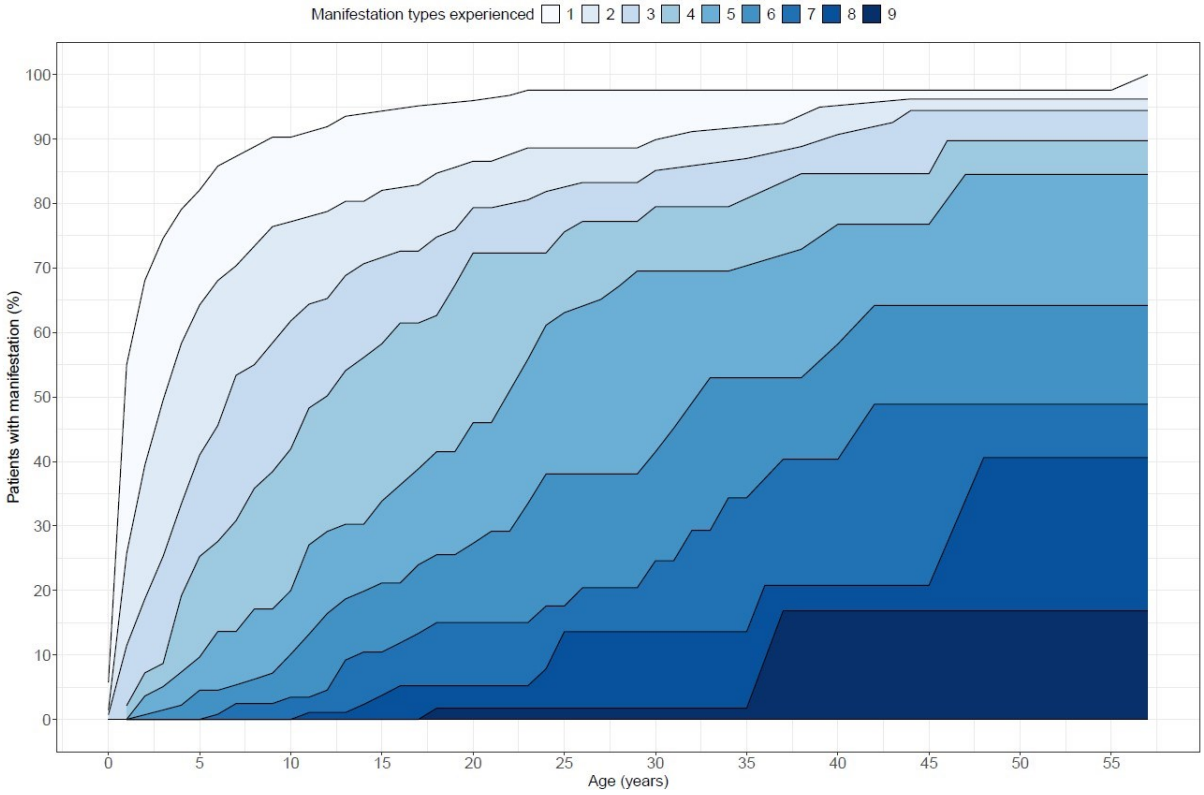
Figure 2. Number of manifestations experienced with age for individuals with APDS in the ESID registry cohort (November 2023 dataset)[a]



Footnote: [a]Manifestation types included respiratory infections, non-respiratory bacterial infections, acute viral infections, chronic viral infections, other infections, antibody-mediated autoimmunity, gastrointestinal disease, lymphoproliferation, malignancy and chronic lung disease. Individuals with missing data were not removed.
Source: Pharming Data on File, 2023.[16]

Mortality

In addition to the substantial morbidity arising from multiple, heterogenous manifestations, published case studies and analyses of the APDS cohort within the ESID registry indicate that APDS is associated with a significant shortening of life, with one in four adults not surviving into early adulthood.[15, 18-20]

- A literature review by Hanson and Bonnen, 2024 identified 256 published cases of APDS and provided evidence on survival. Figure 3 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[19]
- 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).[117] 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.[117] This case series offers the most comprehensive and up-to-date mortality data currently available for individuals with APDS
- The latest analyses of individuals with APDS within the ESID registry indicates that 50% of individuals experienced either malignancy or death by age 40, rising to 73% by age 57, the latest age at which data is available[16]

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- In the Maccari et al., 2023 analysis of the ESID registry (November 2022 dataset), 14 deaths had occurred in the APDS cohort (N=170), with a median age of death of 18.5 years (5–44 years)[13]
- Supplementary cohort studies and literature reviews report 40-year survival estimates ranging from 86% to <60%[12, 15, 18, 20]

Given the recent recognition of APDS as a unique condition and the corresponding recent availability of diagnostic testing,[2] these data may underestimate mortality in this population, as they do not consider the deaths of individuals who died without a definitive diagnosis of APDS.[43] Additionally, 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.[43] 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.[43]

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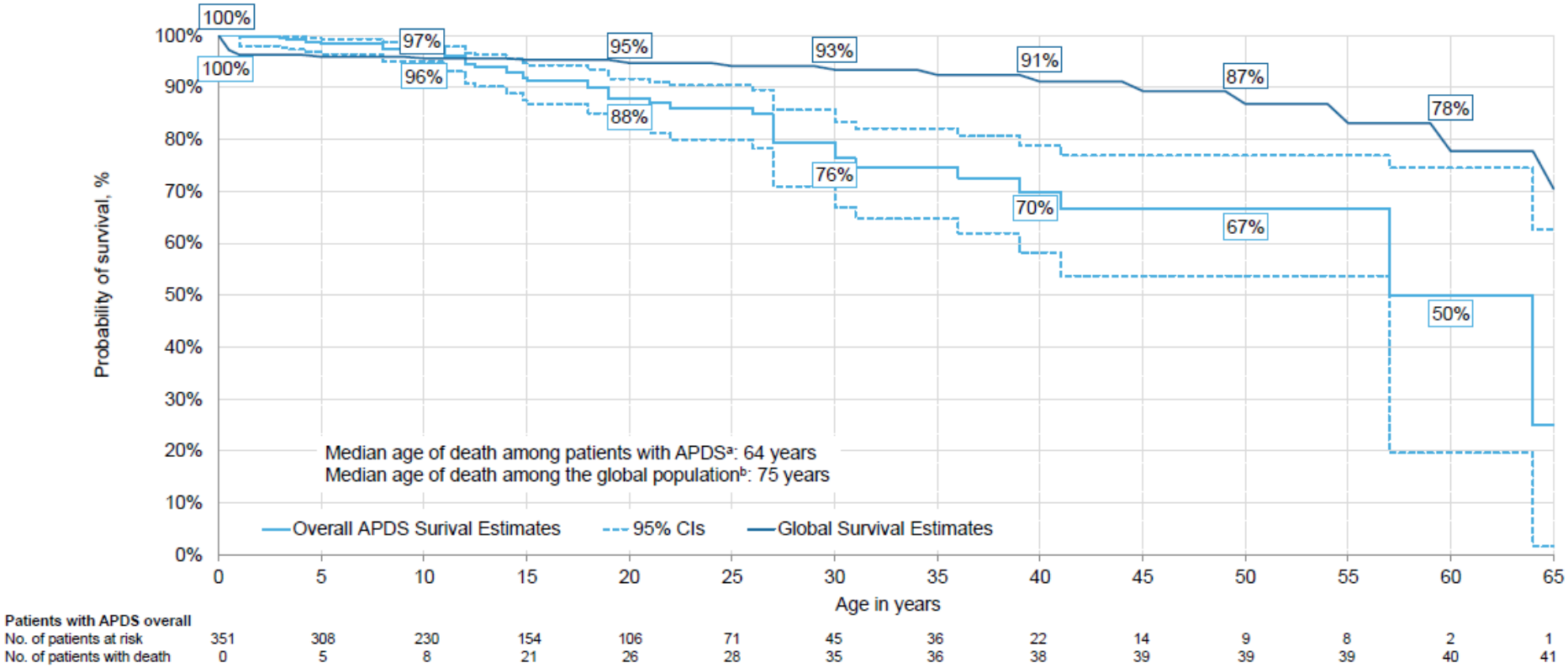
Figure 3. Kaplan-Meier curve of overall survival in individuals with APDS and the global population



Footnote: [a]Median age of death was defined as the age at which 50% of people experienced death. [b]Median age of death for the global population is not presented in the figure.
Abbreviations: APDS: activated PI3Kδ syndrome.
Source: Harrington et al., 2023.[117]

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Accumulation of severe manifestations, increased risk of malignancy, and the adverse effects of current treatments all contribute to early mortality in APDS.[7, 12, 15, 19] Lymphoma is the dominant cause of mortality, resulting in 24–42% of all fatalities seen in APDS (the median age of malignancy diagnosis is 19 years; see 'Malignancy, including lymphoma

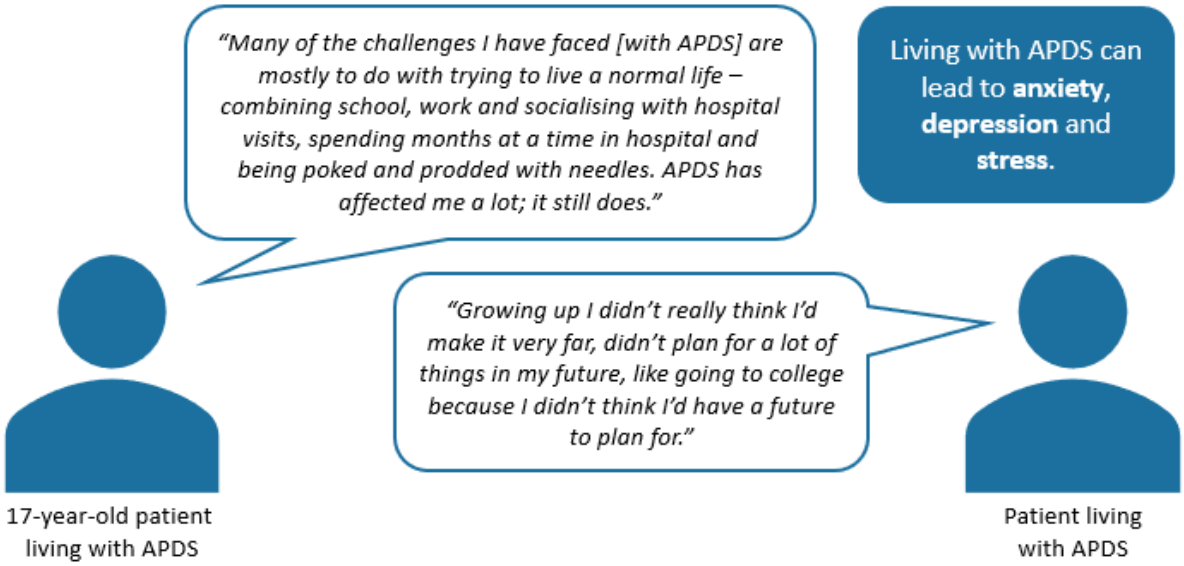
').[10, 13, 19, 107] Non-malignant causes of early mortality in APDS have been reported to include severe respiratory infections, chronic lung infections, respiratory failure, cardiopulmonary arrest, bowel perforation, septic shock, multiple organ failure following HSCT (see 'Allogenic HSCT') and pulmonary haemorrhage.[3, 12, 13, 18, 107]

Clinical manifestations and impact on patient HRQoL

Overall impacts of APDS on patient HRQoL

People with APDS can experience several manifestations simultaneously; the associated symptoms can have cumulative negative impacts on HRQoL.[4, 7, 13, 110] In addition to the high symptom burden, individuals also experience intensive treatment regimens with frequent and prolonged hospital visits with invasive treatments.[3, 13, 15, 29-31] Despite currently available treatments, individuals still face a high risk of developing lymphoma from early in life, and a high risk of early mortality.[13, 18, 19, 105] Living with APDS therefore has broad and substantial emotional impacts on individuals with APDS (see 'Other QoL impacts of APDS' for further detail),[11, 23, 108, 109] as summarised in Figure 4.

Figure 4. Impact of APDS on patient HRQoL



Source: All About APDS,[118] Coulter et al., 2018,[3] Hanson and Bonnen, 2024,[19] Jamee et al., 2019,[18] Pharming Data on File, 2023,[11] Pharming Data on File, 2023,[23] Pharming Data on File, 2023,[115] The Balancing Act, 2023.[26]

Considering the recent recognition of APDS as a disease in 2013 and subsequent sparsity of quantitative data on overall HRQoL impacts, data from other IEIs provide valuable information on the expected impact of APDS on HRQoL. A SLR investigating HRQoL evidence for individuals with IEIs reported that HRQoL was significantly lower in adults with IEIs (mean SF-36 general health score difference: −24.46; 95% CI, −34.57 to −14.34) and children (mean PedsQL total score difference: −10.06; 95% CI, −12.95 to −7.17) compared with the reference population.[119]

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The findings of this SLR are supported by French registry studies: children and adults with IEIs scored significantly lower across most HRQoL domains measured via SF-36 compared with age- and sex-matched general population norms.[120, 121] However, many IEIs do not result in both immune dysregulation and immune deficiency, whereas APDS is characterised by a combination of the two.[3] Therefore, APDS can be expected to have a more substantial and far-reaching HRQoL impact on affected individuals. Further quantitative evidence regarding the impact of APDS on the general HRQoL on individuals receiving current clinical management has been collected to inform the economic model and is presented in Section B.3

Impact of clinical manifestations on HRQoL

Common clinical manifestations associated with APDS are individually discussed below, alongside examples of the impact these individual manifestations can have on patient HRQoL. These examples have been compiled from various sources, including verbatim excerpts where available:

- One-to-one interviews were conducted with individuals with APDS (including four individuals from the UK). These interviews were conducted to inform the development of representative health state descriptions of APDS as part of a HRQoL study, described in Section B.3. The interviews explored APDS from the patient perspective, including patient experiences of manifestations, treatments, and HRQoL impacts[23]
- A narrative account exercise and semi-structured interviews were conducted with 17 individuals and caregivers across the UK, Spain, Australia and the United States, to generate qualitative evidence to explore the burden of APDS[11, 122]
- Patient testimonies available online,[21, 22, 123, 124] as well as clinical opinion[125]

To explore the cumulative negative impact on HRQoL for individuals with APDS who experience multiple concomitant manifestations, Exercise 2 of the Expert Consultancy comprised of four clinical experts completing the EQ-5D questionnaire based on a series of twelve vignettes. Each vignette described a different individual manifestation or combination of manifestations associated with APDS (see Section B.3 for more detail). The resulting utility values demonstrate that clinicians perceive that people with APDS experience substantial HRQoL burden, which is particularly apparent in individuals who experience multiple concomitant manifestations and/or develop lymphoma (Figure 5).[23]

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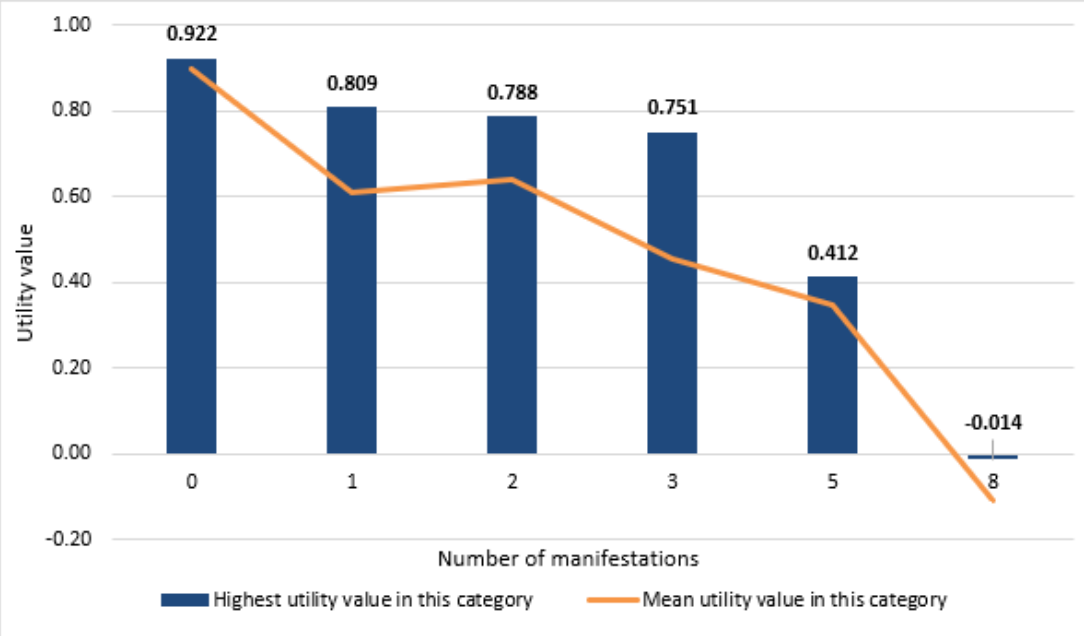
Figure 5. Utility values for health states by numbers of manifestations (highest value within each category and mean value within each category)



Footnote: 0 manifestations: APDS; 1 manifestation: +infections, +lymphoproliferation and splenomegaly, +bronchiectasis, +malignancy; 2 manifestations: +infections+lymphoproliferation and splenomegaly; 3 manifestations: +infections+lymphoproliferation and splenomegaly+malignancy, +infections+lymphoproliferation and splenomegaly+bronchiectasis, +infections+lymphoproliferation+cytopenia +infections+lymphoproliferation and splenomegaly+GI; 5 manifestations: +infections+lymphoproliferation and splenomegaly+bronchiectasis+cytopenia+GI manifestations; 8 manifestations: +infections+lymphoproliferation and splenomegaly+bronchiectasis+cytopenia+GI manifestations+malignancy+fatigue+hearing loss.
Abbreviations: GI: gastrointestinal.
Source: Pharming Data on File, 2023.[23]

Lymphoproliferation (lymphadenopathy), splenomegaly and hepatomegaly

Lymphoproliferation in APDS is where hyperactivity of the PI3Kδ pathway leads to an uncontrolled increase in the number of dysfunctional immune cells.[126] Lymphoproliferation was observed in 70.4% of individuals with APDS in the cohort study by Jamee et al., 2019.[18] In the ESID registry, lymphoproliferation was experienced by 48.0% of the known APDS population by age 5 and 90.0% by age 30 (November 2023 dataset).[16]

Lymphocytes collect in lymphoid tissue and organs within the immune system, which can lead to lymphadenopathy (lymph node swelling).[12, 127, 128] Lymphadenopathy can result in painful and large lymph node swellings across the body (including tonsils and lymph nodes in the chest) and difficulty breathing.[11, 23, 129, 130] Moreover, swollen tonsils and/or adenoids can impact the ability to sleep and eat, with gagging and difficulty swallowing reported.[11] In the Jamee et al., 2019 cohort, 61.3% reported lymphadenopathy and 9.0% had swollen tonsils, while in the Maccari et al., 2023 cohort, 86.0% reported lymphadenopathy as well as enlargement of the spleen (see below).[13, 18]

38-year-old patient living with APDS[11]	*"I had [enlarged] lymph nodes [all over] my body here, even my lower back, and it was really painful. I had trouble standing up straight, it was very painful. It was pressing on my organs and everything"*
Caregiver of a 3-year-old patient living with APDS[11]	*"They would actually make her gag a lot and throw up, so she would end up choking and gagging on stuff because she couldn't swallow very well because of the tonsils"*

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Lymphoproliferation can also lead to enlargement of the spleen (splenomegaly) and/or liver (hepatomegaly).[12, 13, 18] People diagnosed with splenomegaly or hepatomegaly can experience symptoms of fatigue, severe upper abdominal pain and may bruise and bleed more easily.[131-134] Splenomegaly and hepatomegaly have been reported in 47.3% and 28.8% of individuals with APDS in Jamee et al., 2019 cohort study, respectively.[18]

In addition to lymphadenopathy, splenomegaly and hepatomegaly, excessive lymphoproliferation can also result in lymphoid hyperplasia in the respiratory and gastrointestinal tracts, observed in 25% of individuals with APDS in the Maccari et al., 2023 cohort,[13, 135] and can lead to mechanical obstruction, resulting in:

- Recurrent and chronic infections, sleep apnoea and/or need for surgery for the respiratory tract,[136, 137] or
- Dysphagia, diarrhoea, bleeding and rectal prolapse in/from the gastrointestinal tract[11, 12, 138]

Gastrointestinal manifestations

Gastrointestinal manifestations in individuals with APDS may occur as a result of lymphoproliferation (described above), inflammation, and autoimmunity (described below).[12, 13, 135, 139] A recent analysis of the ESID registry highlights that gastrointestinal disease is experienced by 26% of the known population with APDS by age 10 and 61% by age 45 (November 2023 dataset).[16]

- Within the Maccari et al., 2023 cohort, enteropathy, ranging from protracted diarrhoea to inflammatory bowel disease (IBD), was reported in 35% of individuals with APDS.[13]
- Some manifestations (such as protracted diarrhoea) are severe enough in individuals with APDS to require hospitalisation.[6]

Individuals with APDS with gastrointestinal manifestations can experience disabling and frequent symptoms,[11, 123] including struggling with their diet and maintaining weight, stomach pains, requiring a gastronomy tube (G-Tube) for nutrition, as well as chronic diarrhoea, all of which impacts their sleep and daily activities, including work.[11, 21, 23, 124]

- Individuals with APDS can also experience malabsorption as a result of these gastrointestinal manifestations, which can lead to a variety of symptoms such as malnutrition, impaired wound healing, immune deficiency and fatigue.[15, 23, 140]

17-year-old patient living with APDS[21]	*"I think it [APDS] also has an impact on my diet because when I eat something my bowel is immediately affected, it's like my body is trying to get rid of the bad nutrient."*
38-year-old patient living with APDS[11]	*"[I] had my first full time job in last 2011 and that's when my symptoms really started to get worse. Very poor timing, and I was on the toilet so many times during the night I didn't get any sleep, it was affecting my performance at work and I had to resign"*

Autoimmune cytopenia and other autoimmune manifestations

Hyperactivity of the PI3Kδ pathway in APDS drives autoimmune manifestations;[12, 141] 28.4% and 42.0% of individuals with APDS were affected by autoimmune manifestations in the studies by Jamee et al., 2019 and Coulter et al., 2017, respectively.[12, 18]

Cytopenia refers to a lower-than-normal count of blood cells, and can lead to symptoms of fatigue and weakness, easy bruising and bleeding, frequent infections and fever.[142, 143] Types of

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autoimmune cytopenia seen in APDS include low levels of red blood cells (anaemia), neutrophils (a type of immune cell) [neutropenia] or platelets (helps blood clot) [thrombocytopenia such as thrombocytopenic purpura].[144] Autoimmune cytopenias can have negative impacts on energy levels, and can lead to episodes of dizziness, breathlessness whilst carrying out daily activities, as well as an increased risk of bleeding and bruising compared to healthy individuals without APDS.[23, 115, 142, 145, 146] Individuals with APDS with autoimmune cytopenias may often require hospitalisation to receive additional transfusions,[116] and/or supplemental medication such as iron tablets.[115]

- In the Maccari et al., 2023 study, cytopenia affected around 19% of individuals with APDS, with autoimmune origins documented in the majority of these individuals.[13] Cytopenia may also have non-autoimmune origins, for example, as a result of infections, nutritional deficiencies and side effects of medication.[144]
- Analyses of the ESID registry highlighted that 21% of people with APDS experienced autoimmune haematological manifestations by the age of 15, and 38% by the age of 40 (November 2023 dataset).[16]

APDS can give rise to a variety of other autoimmune manifestations in different tissues and organ systems, such as colitis or glomerulonephritis, and people with APDS may experience different types of autoimmune manifestations concurrently.[18]

Malignancy, including lymphoma

By the age of 20 years, 17% of individuals with APDS within the ESID registry had experienced a type of malignancy, and 43% by the age of 40 years (November 2023 dataset).[16]

Lymphoma is the most common type of malignancy in people with APDS:

- Of those who developed malignant diseases in the Jamee et al., 2019 cohort, lymphoma was reported as the most common type of malignancy (89%).[18]
- Analyses of the ESID registry data highlighted that 10% of the people with APDS had experienced lymphoid malignancy (i.e. lymphoma) by the age of 20 years, and 16% by the age of 40 years (November 2023 dataset).[16]
- Individuals being managed for lymphoma often remain undiagnosed for underlying APDS. Therefore, those who develop Ig deficiency post-lymphoma treatment will likely be diagnosed with secondary immune deficiency. As such, these factors indicate that APDS-related malignancies are likely underreported in registries and the literature.[43]
- In addition to lymphoma, other malignancies such as ovary neoplasms, basal cell carcinoma, papillary thyroid carcinoma and multiple myeloma have been reported in individuals with APDS within the literature, but at a lower level.[13, 32, 147] People with APDS have also been reported to have multiple types of lymphomas, or a range of malignancies, simultaneously;[13, 107] lymphoproliferation may play a role in the increased risk of malignancy in people with APDS.[14, 148]

Individuals with lymphoma experience significant psychological distress and impaired HRQoL, including constant anxiety about the occurrence/recurrence of lymphoma, fear of poor response to treatment, social isolation, panic, suffering and death.[23, 111] In additional to the emotional burden associated with lymphoma, following diagnosis, the necessity of frequent and inconvenient hospital visits to receive chemotherapy and have additional blood work, adds additional stress and disrupts their routines and daily lives.[11, 23]

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Alongside the physical symptoms of lymphoma, such as fatigue, pain and night sweats,[112] individuals with APDS and lymphoma may also experience an even higher risk and severity of infections, as lymphoma treatment, such as chemotherapy, can further compromise the immune system.[149]

38-year-old patient living with APDS[11]	*"It would be very meaningful, not having to worry about the lumps, not having to worry about those lumps turning into lymphoma, the pain, obviously. Yes, so that would be nice not to have to worry about that. Quite meaningful, I think."*

Infections and subsequent irreversible end-organ damage

People with APDS can present with a large variety of infections:[70]

- Recurrent respiratory infections are near-universal in people with APDS,[130] with 92% of individuals affected by respiratory infections.[10, 13] These infections are often severe;[10, 24] pneumonia was observed in 62% of individuals with APDS within the ESID registry (mean age at first instance of 9 years old; November 2023 dataset)[16]
- Viral infections, such as persistent, severe or recurrent EBV and CMV infections have been reported in 22% (age range: 1–37 years) and 14% (age range: 1–35 years) of individuals with APDS, respectively. Acute viral infections were also reported in 47% of individuals with APDS[13]
- Fungal infections are also reported in individuals with APDS, such as *Candida albicans* (6.5% of individuals with APDS in the Jamee et al., 2019 cohort) and mycobacterial infections (five individuals with APDS in the Maccari et al., 2023 cohort)[13, 18]
- Certain cases of invasive bacterial infections in people with APDS can lead to life-threatening sepsis[70]

Severe oto-sinopulmonary infections are experienced from a young age.[10, 114] Analyses of the ESID registry data highlight that 83% of people with APDS had experienced chest infections, otitis media (an infection of the middle ear), pneumonia and/or sinusitis by the age of 10 years (November 2023 dataset).[16] Individuals with APDS frequently experience recurrent oto-sinopulmonary infections, presenting with persistent cough, sore throat, high fever, muscle aches and chest pain, severely impacting their HRQoL and ability to carry out their daily activities.[11, 21-25] To prevent recurrent oto-sinopulmonary infections, individuals with APDS typically:

- Require ongoing follow-up and therapy such as IRT and prophylactic antibiotics,[3, 11, 23] which can have a lifelong impact on HRQoL[125]
- Make lifestyle adjustments including practicing social distancing to prevent recurrent oto-sinopulmonary infections; such behaviours result in individuals being unable to go to school or attend milestone events[11, 23]

The combined frequency and severity of recurrent oto-sinopulmonary infections can lead to persistent cough and lung disease.[12, 14, 24, 150] The EMA recognise repeated lung infections, which can lead to bronchiectasis, as contributing to the long-term debilitating and life-threatening nature of APDS (see 'Lung disease, including bronchiectasis-associated airway disease and advanced lung disease' for further detail).[151]

Recurrent severe ear infections may also lead to hearing loss,[12, 152] which was reported in 8% of people with APDS in the Coulter et al., 2017 cohort study.[12] As a result, individuals with APDS

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can struggle with hearing, leading to feelings of frustration because they may be less able to participate in conversation with their families, socialise with friends and/or communicate in the workplace, negatively impacting their day-to-day HRQoL.[23, 123]

Father of a 24-year-old patient living with APDS[123]	*"For many years she has been dealing with endless coughings and colds and she often had to be absent from school due to her infections. Every two weeks we had to go to the doctor to get a prescription for antibiotics. She was afraid to be with her peers and to play with them as she feared to contract flu, with severe consequences on breathing and hearing."*
17-year-old patient living with APDS[11]	*"I fear going to prom, I fear going to graduation, I fear going to a lot of big events because I worry about what I might catch and if I'll come back from it"*
28-year-old patient living with APDS[11]	*"I started on immunoglobulin therapy around age 10, and I had a medi-port placed. Since I had this device placed, I was not able to participate in any sport."*

Lung disease, including bronchiectasis-associated airway disease and advanced lung disease

Causes of lung disease in people with APDS include lymphoproliferation, autoimmunity, as well recurrent and persistent infections (including those of viral origin not susceptible to antibiotics), all of which may lead to airway damage and/or inflammation, weakening the airway wall.[4, 10, 12, 43, 130]

Bronchiectasis is defined as abnormal, permanently dilated airways.[153] Bronchiectasis typically occurs early in the disease course (during early adolescence) and is one of the most common and severe consequences of recurrent infections in APDS:[3, 4, 12]

- In the Maccari et al., 2023 analysis of the ESID registry (November 2022 dataset), bronchiectasis was reported in 50.0% of individuals with APDS (cohort age range: 1–43 years old; median age 7 years)[13]
- Even higher rates have been reported; more recent analyses of the ESID registry identified that bronchiectasis was experienced by 40.0% of the known APDS population by the age of 15, and 70.0% by the age of 45 (November 2023 dataset)[16]
- Supplemental evidence from a SLR by Jamee et al., 2019 reported bronchiectasis in 28.4% of individuals with APDS (cohort age range: 6.5–21.5 years old)[18]

Bronchiectasis-associated airway disease encompasses individuals with bronchiectasis and/or other pulmonary manifestations, some of which may not be permanent.[14] Individuals with APDS report that lung disease can negatively impact their energy levels and result in sleep apnoea (where breathing stops and starts during sleep), impacting their ability to complete personal leisure activities and day-to-day tasks, leading to feelings of frustration.[11, 23, 113] Bronchiectasis-associated airway disease can lead to individuals with APDS to struggle with their breathing, experience chest pain and need supplementary pulmonary support.[11, 23, 47, 48, 64] Moreover, individuals with APDS and lung disease often face regular time-consuming hospital appointments for monitoring, and experience anxiety about the irreversible end-organ damage and scarring they have experienced.[11, 23]

Advanced lung disease is a subset of bronchiectasis-associated airway disease that has a substantial impact on mortality and/or HRQoL.[43] The FEV1/FVC ratio is often used to assess the severity of lung disease, and FEV1 or FEVC <70% and <50% indicates obstructive and severe lung disease, respectively.[113, 154] Analyses of the ESID registry data highlighted that 5% of the people with APDS had experienced severe lung disease (defined as a record of bronchiectasis

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with FEV1 or FVC ≤70%) by the age of 20 years, and 36% by the age of 40 years (November 2023 dataset).[16] In severe cases, advanced lung disease can progress and lead to death from respiratory failure in its end stages.[12, 19]

Patients living with APDS[23]	*"…obviously it's the lung damage side the obviously breathing harder especially when it's cold"*
	"I'm well aware that PI3K effects the structure of my lungs, there's repeating scarring that I can get from my asthma…"

Other multi-system manifestations

As PI3Kδ is also expressed outside of the immune system, hyperactive PI3Kδ activity may also result in other multi-system manifestations in people with APDS.

- Supporting the potential role of PI3Kδ in neurological development, symptoms of neurodevelopmental delay have been reported in people with APDS, including isolated speech or language delay, mild cognitive impairment, learning disabilities, anxiety and depressive disorders, autism-like spectrum disorders and behavioural issues[10, 12, 13]
- Individuals with APDS typically have lower educational achievements which cannot be accounted for by chronic illness effects[14]
- Allergies and asthma are common in individuals with APDS, as the PI3K pathway is thought to contribute to allergic airway inflammation in asthma in human bronchial epithelial cells.[51, 155] Asthma manifests as shortness of breath, coughing and wheezing; symptoms of more general allergy include nausea and diarrhoea[156, 157]

Other QoL impacts of APDS

Fatigue

Fatigue is common amongst individuals with IEIs.[108, 109, 158] In APDS, the cumulative impact of manifestations can lead to symptoms of low energy, tiredness and muscle aches.[23] In qualitative interviews individuals with APDS reported that they had a "constant lack of energy" and "just crushing fatigue".[11] As such, individuals were frequently tired after exercise but also after daily activities, such as decision-making at work and/or cooking meals.[23] These interviews are supplemented by public statements from individuals with APDS who report feeling "exhausted" and "drained, both mentally and physically".[21, 22, 124]

Mental health, including anxiety

APDS also has a negative psychological impact on individuals with the condition.[11, 23] A recent study performed in the Netherlands concluded that mental health is compromised in people with IEIs such as APDS, due to fear of infections, social isolation, maladaptation to illness and concerns over the future impact of their illness.[159, 160] The proportions of individuals with an IEI reporting moderate or high levels for each dimension (33.9% distress, 18.9% depression, 22.4% anxiety, and 36.2% somatisation) were significantly higher ($p<0.001$) than those of the age-matched control individuals (16.3% distress, 5.7% depression, 8.0% anxiety, and 11.2% somatisation). This evidence aligns with findings from qualitative interviews with people with APDS, who reported feeling sad, isolated, socially isolated and frustrated as a result of living with APDS. 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.

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These negative impacts on mental health can lead to difficulties in making friends and maintaining interpersonal relationships.[11, 23, 26]

36-year-old patient living with APDS[123]	*"My mental health has been put to a hard test and, although a private psychological support, I'm going on fighting with permanent anxiety relevant to the fact that my body could let me down at any moment."*

Social impact

In Exercise 4 of the Expert Consultancy, five clinicians estimated that on average for 18.50 days of the year (range: 10.00–30.00 days) individuals with APDS are unable to work or participate in education due to in-patient visits, with further weeks of absence due to infectious or inflammatory illnesses.[14]

Caregiver impact

Many people with APDS require physical and emotional support from caregivers who may, in turn, be impacted by the stress of caring for family members with APDS, possibly having APDS themselves. Of the nine caregivers who participated in qualitative interviews, all described the negative impact that their caring responsibilities have had on their emotional wellbeing (including reports of depression, anxiety and anger) as well as on their daily activities, such as having to reduce working hours to attend hospital appointments and/or manage medical issues (e.g. G-Tube being dislodged).[11]

The negative impacts on caregivers' relationships, physical health, emotional wellbeing and family life associated with living with and supporting an individual with APDS were highlighted across the interviews. For example, caregivers reported that their caregiving responsibilities lead to restrictions on family holidays, with the concern that certain destinations have greater risk of infections, in addition to logistical difficulties such as working around treatment schedules.[11, 123]

Caregiver of 10-month-old patient living with APDS[123]	*"It's meant that I've possibly missed some employment advancement opportunities because of my absence, and it also can cause a bit of strife with co-workers who happen to pick up my end of the workload… in my absence."*
Caregiver of 3-year-old patient living with APDS[123]	*"We don't get together with people like we used to, just because either A, it's not exposing her to other stuff, or we're too tired to or she just is not feeling up to it, and so then we cut that out."*

Epidemiology

APDS is an ultra-rare condition, with recent literature reporting that APDS affects between 1–2 per 1,000,000 individuals globally.[4] In alignment with this estimate, there are [redacted] patients (of all ages) with APDS currently enrolled in the UKPID registry in England (as of 30th April 2024).[161]

The English clinical immunology community acknowledges that multiple people with APDS have died over the past five years, including some individuals never included within the registry. Based on Pharming medical field-team insights, and considering that not all individuals are enrolled into the UKPID registry, it is estimated that there are approximately [redacted] people with APDS in England, of which [redacted] are aged 12 years and older.

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Furthermore, it is believed that some individuals, particularly adults presenting to clinicians prior to 2021, may not have had a genetic test and so have been managed with the less specific diagnosis of common variable immune deficiency.[43] Consequently, as part of the Expert Consultancy project (Exercise 4, Quantitative), clinical experts were asked to estimate the increase in incident diagnosed cases of APDS per year in England (for those aged 12 years and older), following the positive recommendation of a PI3Kδ-specific inhibitor by NICE. On average, the clinicians estimated a 2.5% annual increase in Year 1, rising to an 8.83% increase in Year 5.[14]

B.1.4.3 Current and future treatment pathway

Summary

- There are currently no licensed treatments available for APDS in the UK that target the root cause of disease. Current management in the UK is limited to supportive care, and polypharmacy approaches are required to manage the multiple manifestations and symptoms associated with immune dysregulation and/or immune deficiency.[3, 13, 14, 17, 18, 27, 28]
- Treatments commonly include IRT, antimicrobial treatment, multiple lines of immunosuppressive therapies and surgical interventions and other procedures.[3, 13, 14, 17, 18, 27, 28]
- There is no specific guidance on if and when clinicians should perform HSCT for people with APDS.[43] HSCT may be considered with curative intent for specific individuals with APDS, for example, those with severe disease progression (e.g. lymphoma), younger individuals to prevent future APDS-related complications, or where there are concerning risks with long-term use of treatments.[3, 14, 43, 162, 163] Despite judicious use and expertly-led clinical management, HSCT carries a two-year mortality risk of 10–20% in people with APDS and is associated with significant morbidity risks,[3, 19, 32, 164] with engraftment failure seen in up to 36.4% of individuals.[20]
- Current treatments do not target the root cause of APDS therefore, despite current clinical management,[3, 13, 165] individuals with APDS continue to experience disease progression and potentially life-threatening manifestations, resulting in a reduced quality of life and life expectancy compared with people without APDS.[3, 12, 13, 15, 18]
- Treatments for immune dysregulation are immunosuppressive, and therefore exacerbate immune deficiency in individuals with APDS, leading to cyclical polypharmacy approaches.[3, 6, 27] Additionally, current treatments are associated with frequent and/or severe side effects, invasive administration methods, and regular hospital-based administration.[3, 13, 15, 29-31] With many treatments prescribed long-term, the adverse impacts of treatments occur lifelong.[5, 14, 30, 31, 125, 166]
- The substantial limitations of current management highlight an unmet need for a generally well tolerated, licensed disease-modifying treatment that targets the underlying hyperactive PI3Kδ enzyme complex,[167] addressing the range of manifestations leading to improvements in HRQoL and mortality.
- Leniolisib is the first targeted therapy for APDS which selectively inhibits the catalytic subunit of the PI3Kδ enzyme complex, addressing the hyperactivity of the enzyme and restoring signalling homeostasis in the PI3Kδ pathway. This targeted mechanism of action allows leniolisib to treat the underlying cause of APDS, improving both the immune dysregulation (e.g. lymphoproliferation) and immune deficiency (e.g. severe,

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recurrent and/or persistent infections) observed.[9, 17, 27, 33-35] In turn, this leads to improvements in HRQoL, improving an individual's energy levels and ability to complete daily activities, as well restoring their hope and general wellbeing.[17, 26, 35-37] As leniolisib has the potential to prevent and reverse the progression of manifestations, prevent irreversible end-organ damage, and spare and/or halt the use of multiple symptomatic treatments, we expect that leniolisib will be prescribed following diagnosis in individuals aged 12 years or older.

Diagnosis and clinical care teams

Alongside assessment of clinical symptoms and laboratory testing, individuals who are suspected to have APDS are currently directed by clinical immunologists towards genetic testing.[168, 169] The R15 test covers over 300 genes related to IEIs, including *PIK3CD* and *PIK3R1* (the genes affected in APDS),[170] which were added to the panel in 2017.[43] The R15 test has been standard practice in the NHS to support diagnoses for individuals with suspected IEIs.[2, 43] The use of this test ensures that individuals are tested for a wide range of IEIs at once, including APDS, minimising the risk of misdiagnoses.[170] The introduction of leniolisib is not expected to change the existing diagnostic pathway for APDS.

Specialist services such as paediatric immunology or paediatric pulmonology may be available to manage children with APDS in the UK, depending on the hospital.[43] Clinical immunologists manage adults with APDS in the UK, and oversee appropriate specialist input for each impacted organ system, forming a multi-disciplinary care team.[14, 25] Results from the quantitative survey conducted for the Expert Consultancy (Exercise 4) indicated that individuals with APDS would require on average 1.6 (range 1.0–2.0) multidisciplinary team assessments per year, in addition to frequent visits to clinical immunologists, GPs, respiratory specialists, specialist airway radiologists, gastroenterologists, haematologists, genetic counselling, outpatient infusion centres, physiotherapists, psychologists and rheumatologists. The clinicians involved in patient care will depend on the organ systems affected, treatments being considered/used and patient needs.[14] The introduction of leniolisib is not expected to alter clinical care teams for APDS.

Overview of current treatment pathway

There are currently no licensed treatments available for APDS in the UK. Along with manifestations, procedural burden increases with age in individuals with APDS; in the ESID registry, treatment rates reach 79% by the age of 20 years in individuals with APDS (Figure 6). Current management is limited to supportive care that commonly includes combinations of IRT, antimicrobial treatment, multiple lines of immunosuppressive therapies, and surgeries and other procedures (see Figure 7).[3, 13, 14, 17, 18, 27, 28]

Given the recent identification of APDS as a unique disease in 2013,[2] there are currently no UK guidelines for the management and treatment of APDS and Sweden is the only European country that has developed such at this time.[171] With APDS manifestations simultaneously affecting multiple organ systems, and current treatments each only addressing specific manifestations, treatment combinations need to be carefully tailored to each individual's needs.[3] For example, individuals with APDS are often prescribed multiple immunosuppressive therapies, with some individuals receiving two or three separate medications before the age of 10.[6]

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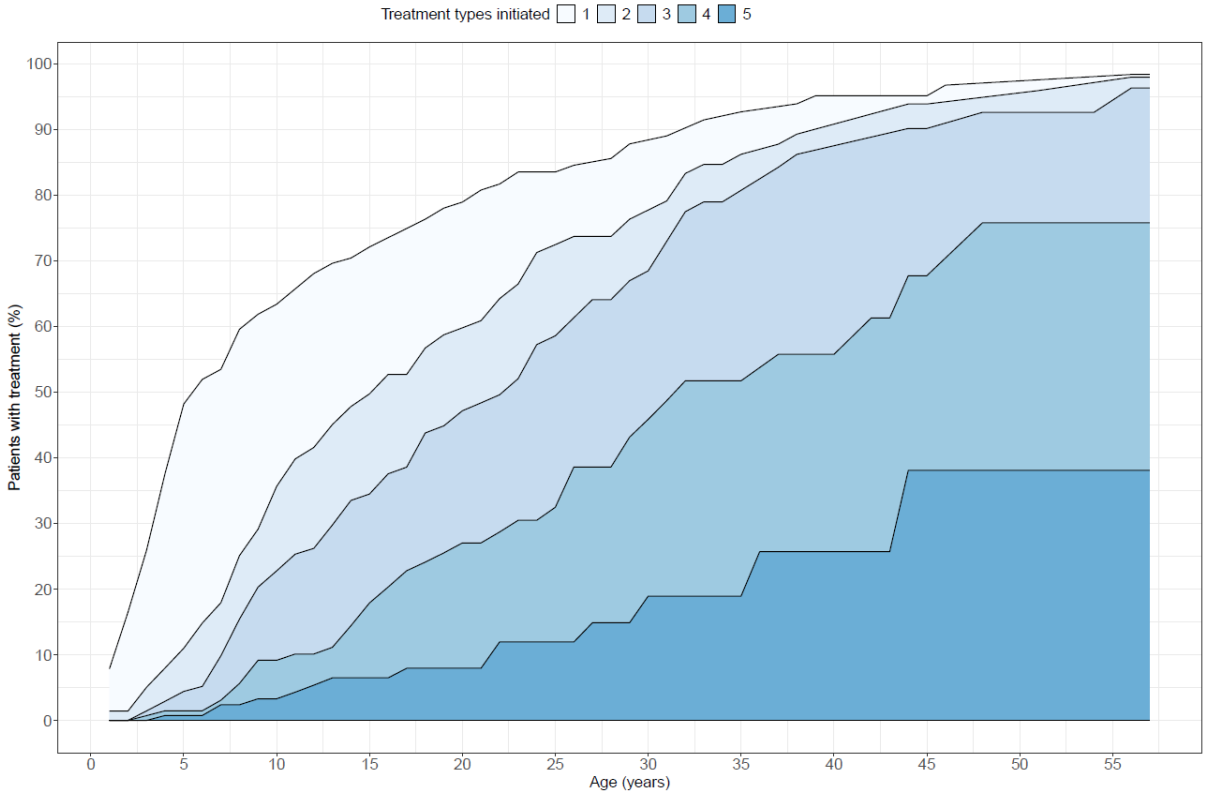
Figure 6. Number of treatments with age for individuals with APDS in the ESID registry cohort (November 2023 dataset)[a]



Footnote: [a]Treatment types included corticosteroids, HSCT, immunosuppressants, splenectomy, tonsillectomy. IRT and antibiotics were not included as these outcomes did not have associated dates. Individuals with missing data were not removed.
Abbreviations: APDS: activated phosphoinositide 3-kinase δ syndrome; HSCT: haematopoietic stem cell transplantation; IRT: immunoglobulin replacement therapy.
Source: Pharming Data on File, 2023.[16]

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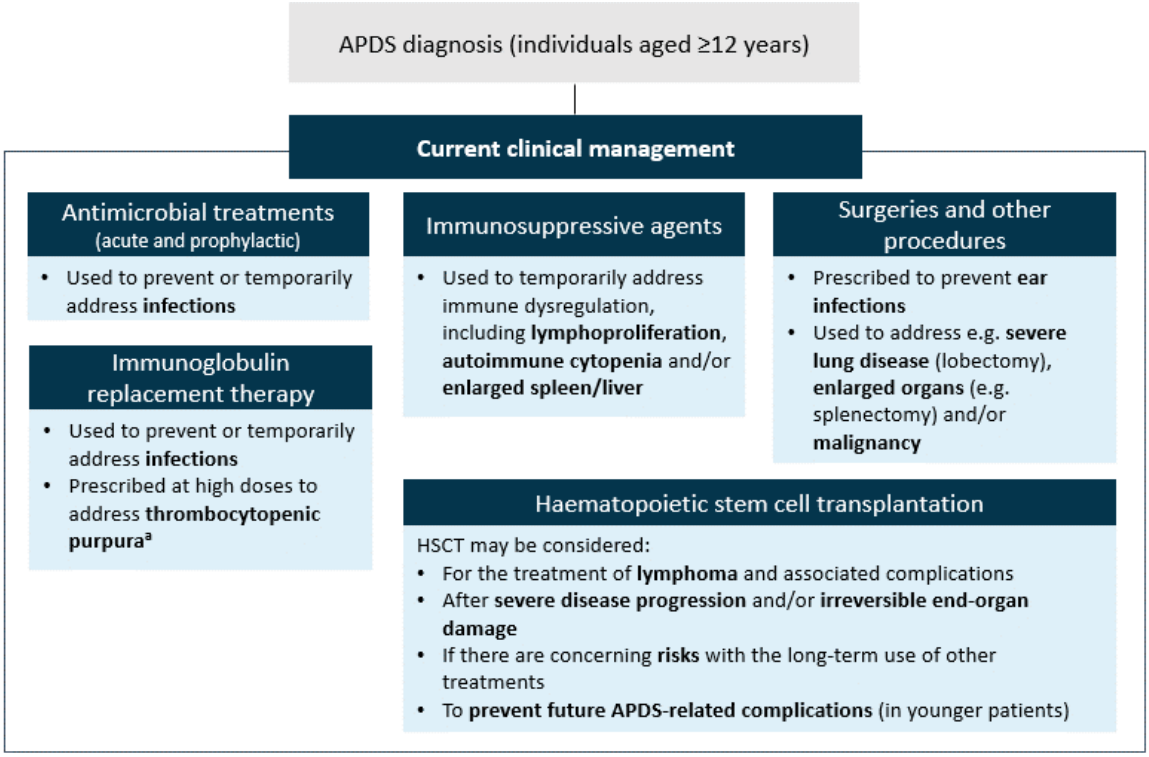
Figure 7. Overview of the current treatment pathway for APDS



Footnote: Blue boxes summarise the treatment description, whereas yellow boxes detail the main limitations of the treatment. [a]Thrombocytopenic purpura is a blood disorder characterised by a decrease in the number of platelets in the blood.
Abbreviations: APDS: Activated PI3Kδ syndrome; mTOR: mammalian target of rapamycin.
Source: Bloomfield et al., 2021,[106] Bride et al., 2016,[172] British Thoracic Society, 2018,[173] Castagnoli et al., 2019,[174] Cerny et al., 2002,[175] Condliffe et al., 2018,[130] Coulter et al., 2017,[12] Coulter et al., 2018,[3] Dimitrova et al., 2022,[32] Elkaim et al., 2016,[15] Gobert et al., 2011,[176] Hanif, 2022,[177] Hansen et al. 2004,[178] Hemming, 2001,[179] Immune Deficiency Foundation,[180] International Patient Organisation for Primary Immunodeficiencies,[24] Jamee et al., 2019,[18] Katragkou et al., 2018,[181] Lougaris et al., 2021,[182] Lucas et al., 2014,[29] Masters et al., 2003,[183] McKay et al., 2003,[184] Okano et al., 2019,[20] Palavra et al., 2017,[185] Pharming Data on File, 2022,[5] Pharming Data on File, 2023,[14] Preite et al., 2019,[186] Singh et al., 2018,[187] Singh et al., 2020,[28] Vanselow et al., 2023,[4] Youssef et al., 2016.[188]

Limitations of current clinical management

Current treatments are associated with several limitations, as explored in further detail in the following sections:

- Current treatments do not target the root cause of APDS and only temporarily address APDS manifestations and symptoms.[3, 13, 165] This means that long-term use of multiple treatments to manage individual symptoms is often required.[5, 14, 27, 166] In turn, this results in a lifelong high treatment burden for individuals with APDS
- Despite current treatments, individuals continue to experience infections and disease progression, resulting in irreversible end-organ damage, such as advanced lung disease and/or hearing loss, as well as early mortality, for example, due to lymphoma or bronchiectasis;[3, 6, 12, 14, 19]

  - The progression of lymphoma in people with APDS significantly worsens their prognosis, underscoring the necessity of proactive and preventative treatments, according to clinical opinion[43]

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- Treatments for immune dysregulation are immunosuppressive, thereby exacerbating immune deficiency, leading to cyclical polypharmacy approaches in an attempt to manage both immune dysregulation and immune deficiency;[3, 6, 27]
- Current treatments are associated with frequent and/or severe side effects, are invasive, and often require multiple hospital visits for administration, impacting patient HRQoL[3, 13, 15, 29-31]

IRT

Individuals with APDS typically begin receiving IRT between 5–10 years of age.[15, 31] Up to 89% of people with APDS eventually receive long-term IRT; long-term treatment is required as IRT only temporarily replaces antibodies.[3, 12, 15, 180] More specifically in the UK, IRT is used in all people with APDS who have evidence of a functional or qualitative antibody deficiency (e.g. demonstrated by poor vaccine responses, infections, abnormal antibody titres or poor quality antibodies).[5]

IRT contains 95–98% pure IgG, and therefore does not address deficiencies of other Igs in APDS, such as IgA.[180] Accordingly, an analysis of the UKPID registry (n=139; dataset date not reported) demonstrated that despite use of IRT, 78% of individuals with APDS suffered from bacterial infections, 74% from pneumonia, 70% chronic sinusitis, 38% otitis and 23% conjunctivitis; 56% also had bronchiectasis.[189] Additionally, whilst IRT is reported to address thrombocytopenic purpura by raising platelet counts (see 'Autoimmune cytopenia and other autoimmune manifestations'),[178] expert opinion highlights the need for high doses of IRT for this to be successful.[43] Moreover, IRT has poor effectiveness in treating viral infections,[43, 190] is not known to address other autoimmune cytopenias, or prevent other immune dysregulation aspects of APDS such as lymphoproliferation or lymphoma.[3, 182] People with APDS continue to experience disease progression despite use of IRT, requiring additional therapies such as immunosuppressive agents.[3, 189, 191]

An invasive, blood-based infusion, intravenous administration of IRT (IVIG) is typically administered in a hospital every two, three, or four weeks;[31] 35.2% (37/105) of individuals with APDS observed in the ESID registry utilise IVIG recorded at their last visit (November 2023 dataset).[16] Each infusion lasts approximately two to four hours with a follow-up of up to four hours, and individuals with APDS and their caregivers additionally spend long periods of time travelling to and from infusion sites, impacting their HRQoL (see Other QoL impacts of APDS' for further detail).[11, 23, 31] Subcutaneous IRT (SCIG) allows individuals to administer weekly smaller doses of Ig via an injection into the skin and can be administered at home;[54] 64.8% (68/105) of individuals with APDS observed in the ESID registry utilise SCIG (November 2023 dataset).[16] Each infusion can last approximately 2–5 minutes (using manual push) or up to 60 minutes (when using a weekly pump) and can present various logistical challenges for people with APDS when travelling,[54, 192] adding to their daily management burden. Individuals with APDS may also require blood tests to measure Ig levels between infusions.[180] For those people with APDS who face difficulties with needles or their veins, IRT may not be the most suitable treatment option.[54]

People undergoing IRT treatment may experience burdensome side effects from the intravenous injections such as rashes, fever, itching, shivering and headaches.[54] IRT may also lead to more serious side effects, including renal impairment, thrombosis, transfusion-related acute lung injury and arrhythmia.[193] With IRT treatments, there is also a theoretical risk for the transfer of new infections and disease, for example, the spread of prions via IRT can lead to fatal neurological disorders.[54]

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An increase in the global demand for IRT has been reported;[194] additionally, the availability of immunoglobulin products is not always guaranteed. During COVID-19 pandemic, a decrease in plasma donations led to a 14% decrease in UK supply of Ig for several months.[195] Plasma donations continue to be a significant subject of discussion, with recent events in parliament aimed at increasing awareness of existing shortages and promoting self-sufficiency within the UK.[55] Due to plasma shortages, switching between IRT products may be required,[195] which can result in side effects such as headaches and tiredness.[196] Reducing or halting the need for IRT would therefore be beneficial to individuals with APDS as well as the UK healthcare system.[197, 198]

Antimicrobial therapies

Antimicrobial treatments are used as prophylaxis (to prevent infections from occurring) or as acute treatment (to manage severe and sudden onset infections) for APDS in the UK.[3, 199, 200] Antibiotics may be used to treat or prevent some types of bacterial infection. However, they have limited effectiveness for viral infections.[43, 201] Long-term, prophylactic antibiotic treatment is also recommended for adults with bronchiectasis who have three or more exacerbations per year (defined as increases in respiratory symptoms such as cough, sputum production, malaise, fatigue and breathlessness, lasting several days), to prevent further lung damage.[166, 202, 203]

- Antibiotics were administered prophylactically to 61–79% of individuals with APDS in various published cohort studies[6, 12, 15]
- Prophylactic antifungal and antiviral use was reported in 3% (4/136) and 15% (20/133) of people with APDS in the ESID registry (November 2023 dataset), respectively[16]

Antimicrobial prophylaxis does not fully prevent infections for most people with APDS, or address the underlying cause of disease; therefore, disease continues to progress.[28, 204] Hence, individuals with APDS often receive combined IRT and antimicrobial prophylaxis,[3] and rarely receive antimicrobial therapy in isolation.

Common side effects of antimicrobials include diarrhoea, nausea and vomiting, which may add to the gastrointestinal symptoms of APDS that some individuals with APDS already experience (see ‘Gastrointestinal manifestations’). As antibiotics also target protective bacteria within the body, infections of the mouth, digestive tract and vagina can occur during their use. Some people may also have allergic reactions to antibiotics, causing swelling of the face, itching and skin rashes.[199]

The long-term and high frequency use of antimicrobials in combination with continued infections may contribute to antimicrobial resistance, one of the most pressing global challenges currently being faced.[58] Antimicrobial resistance poses a substantial threat to individuals with APDS as it can lead to breakthrough antimicrobial-resistant infections, as well as to worse outcomes with surgeries.[205, 206] NICE antimicrobial stewardship and current NICE guidance (e.g. for bronchiectasis) advise to not routinely offer antibiotic prophylaxis, in line with NHSE’s National Action Plan to tackle antimicrobial resistance.[57, 207] Therefore, alternative treatments options are needed for people with APDS, to reduce reliance on antimicrobial prophylaxis.

Immunosuppression

Immunosuppressive treatments are frequently prescribed to individuals with APDS to help manage immune dysregulation:

- In the Maccari et al., 2018 study, more than half of people with APDS in the cohort had received steroids before the age of 20[6]

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- In the ESID registry, use of rituximab has been reported in 11% (13/115) of individuals with APDS (November 2023 dataset)[16]
- In the ESID registry, 47% (54/116) of individuals with APDS have reported use of mTOR inhibitors (sirolimus), similar to findings in the Maccari et al., 2018 cohort[6, 16]

However, due to their modes of action, individual immunosuppressive treatments cannot address all aspects of immune dysregulation in APDS, and response to treatment varies:

- Steroids inhibit lymphocyte activity and proliferation, addressing the aspects of immune dysregulation related to lymphoproliferation,[184, 208] whilst also increasing susceptibility to infections
- Rituximab induces B cell death,[175, 177] acting only on aspects of immune dysregulation caused by B cell imbalances
- mTOR is positioned downstream of the PI3Kδ enzyme in the PI3Kδ pathway,[209] so mTOR inhibitors only address some of the downstream effects of the hyperactive enzyme complex.[9, 186] mTOR inhibitors are generally prescribed in combination with prophylactic treatments for immune deficiency, for example, in the ESID registry, of the 39 individuals on immunosuppressants, 73% (29/39) have also received both IRT and antibiotics; only two individuals had only received immunosuppressants.[16] However, people still experience disease progression including infections, gastrointestinal symptoms and cytopenias during mTOR treatment.[3, 6, 12, 15]

By inhibiting immune cell activity and promoting B cell death, immunosuppressives cause antibody deficiencies,[210] and thereby exacerbate immune deficiency in APDS. This can result in an increased susceptibility to serious infections,[176, 185, 188] and a cycle of polypharmacy approaches to manage multiple manifestations.[3, 6, 27] Other side effects of immunosuppressive treatments can also be serious, if not fatal:

- Long-term high-dose steroid use is associated with severe gastrointestinal manifestations, osteoporosis and elevated blood pressure,[211] as well as an increased risk of malignancy,[212] which can lead to non-compliance to the steroid treatment regime[213]
- Allergic, anaphylactic reactions were seen in 80–90% of individuals receiving rituximab in randomised controlled trial (RCT), ranging from mild to life-threatening in severity, and infusion reactions can also be fatal[177]
- People treated with sirolimus often do not tolerate the treatment. Side effects include liver toxicity, thrombosis, high cholesterol, anorexia, renal toxicity, hyperglycaemia, cytopenias, stomatitis, skin eruptions, poor wound healing and pneumonitis, lead to treatment pauses or discontinuation.[6, 210, 214-216] Moreover, posterior reversible encephalopathy syndrome has been linked to mTOR inhibitor use in the UK[43, 217]
- Additionally, co-administration of sirolimus with antimicrobials can lead to drug interactions[210]

If mTOR inhibitors are not well tolerated or cause increases in the incidence of infections, cyclosporin can be prescribed to reduce lymphoproliferation. If cyclosporin is also not well tolerated, treatment with mycophenolate mofetil can be attempted.[148, 185] As both these treatments are immunosuppressive, they are associated with the common limitations of immunosuppressive therapies such as increased rates of infections.[218, 219] There is an unmet need for a targeted treatment that addresses both the immune dysregulation and immune deficiency associated with APDS.

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Of note, the NHS Medicines Optimisation Executive Group aims to enhance hospital productivity and support broader social and economic growth in 2023/24 by reducing the demand for rituximab treatments, which are time-consuming to administer and place capacity strains on the NHS, thereby freeing up hospital beds and staff resources.[43]

Surgical procedures

In the ESID registry, tonsillectomy was reported in 46% of individuals with APDS (62/135; November 2023 dataset);[16] however, only 28% of individuals from Maccari et al., 2018 saw a benefit after undergoing tonsillectomy,[6] demonstrating its limited effectiveness. In addition, an increased risk of upper respiratory infections has been demonstrated with this treatment over the long-term,[220] as well as risks for post-operative haemorrhage.[221]

Other surgeries such as splenectomy, lobectomy and ear tube insertion are less commonly used, to address organ enlargement or damage, or to resect malignant tumours in individuals with APDS.[14] In Exercise 4 of the Expert Consultancy, five clinicians noted that adolescent and adult individuals with APDS would experience a wide range of surgeries, including but not limited to tonsillectomy, bronchoscopy, splenectomy, lymph node biopsies and excisions and lobectomy. Please refer to the Expert Consultancy report for further detail.[14]

Surgeries do not address the underlying cause of APDS, and for any surgery received, people can experience AEs such as post-operative infections.[30] In particular surgeries involving drains to remove body fluids or prevent abscesses can heighten infection risk due to the immune deficiency aspect of APDS.[222] Additionally, surgery may generate anxiety and stress for paediatric individuals, which is specifically related to pre-surgical injection, undergoing anaesthesia and coping with post-operative discomfort.[223]

Allogenic HSCT

There is no specific guidance on if and when clinicians should perform HSCT for people with APDS.[43] Access to, and subsequent success of, HSCT is limited by a lack of availability of appropriately matched donors (see Section B.1.5).[60, 163, 224] Additionally, as a result of the life-threatening complications and morbidities associated with HSCT, this procedure is generally not suitable past adolescence; HSCT is performed sparingly in individuals aged 12 years and older.[43, 225-227] In light of the limitations of HSCT (discussed further below), the procedure is therefore only considered by an expert multi-disciplinary team in the UK when there is an appropriate consenting donor, as well as:[3, 14, 43, 162, 163]

- For the treatment of lymphoma and associated complications; or,
- After severe disease progression and/or irreversible end-organ damage, with no or insufficient response to the currently available conventional therapies; or,
- When long-term use of conventional therapies is judged to be inappropriate due to concerning risks (e.g. in the paediatric immunology community, HSCT is considered for any individual that will otherwise require mTOR inhibitor treatment for more than 24 months); or,
- The individual is young and early HSCT may prevent future APDS-related complications and increase the chance of a successful HSCT outcome.

Despite judicious use and expertly-led clinical management, HSCT carries a two-year mortality risk of 10–20% in people with APDS, with Hanson and Bonnen, 2024 reporting HSCT as the second most common cause of death in APDS.[19] Common causes of death from HSCT include sepsis, multiorgan failure, CMV/adenovirus pneumonitis and idiopathic pneumonitis.[18]

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Currently, there is a lack of long-term UK-specific data on individuals with APDS following receipt of HSCT. Available evidence in APDS primarily comes from an international study by Dimitrova et al., published in 2022.[32] However, it's important to note that these data might not offer a comprehensive overview, as the research was conducted retrospectively. In a cohort of 57 individuals with APDS, the two-year probability of overall survival from first HSCT was 86%, with 63% of the deaths occurring in the first 100 days post-HSCT (median follow-up: 27 months).[32] Additional supportive evidence from the NHS England review of HSCT use in individuals with IEIs indicates that overall survival ranges between 54% and 100% for 158 individuals with IEIs post-HSCT (median follow-up [where reported]: 14 months and five years).[163] Risk factors for mortality include chronic GVHD, comorbidities, advanced disease stage (in leukaemia) and second or later transplant;[228-232] these risk factors, mainly infections and neoplasms, are common features of APDS.[18] Experience with HSCT tends to improve over time for other IEIs, however, such improvement has not yet been reported for APDS, underscoring the need for future registry analyses to offer a more comprehensive understanding.[43]

In addition to mortality risks, adverse complications of HSCT are seen in ~90% of people with APDS, and outcomes are poorer in APDS than in other IEIs:[20, 32, 163, 233]

- Engraftment failure is seen in up to 36.4% of people,[20] and graft-failure-free survival drops to 68% after two years in people with APDS.[32] A second allogeneic transplant is the only potential long-term curative option for individuals with graft failure, as demonstrated by the data from the UKPID registry above[234]
- Unstable chimerism or poor graft function is observed in 23% of individuals[32]
- Unplanned cell infusions or multiple HSCT are required in 32% of people with APDS[32]
- Acute graft-versus-host disease (GVHD) is experienced by 39% of individuals,[32] and is associated with increased hospitalisation rates, though it can resolve with appropriate management and care[235, 236]
- Chronic GVHD is experienced by 16% of individuals however,[32] successful treatment options for chronic and/or severe GVHD are sparse[43]

In the ESID registry, HSCT has been reported in 21.1% (November 2023 dataset) of individuals with APDS, with some individuals receiving two or three transplants.[16] Based on data from the UKPID registry (25th March 2024), 17 people from the UK with APDS have received 23 HSCTs (indicating multiple transplants for some individuals), at a median age of 8.53 (interquartile range: 5.00–15.30 years).[43]

HSCT is also a highly invasive and intense treatment, involving a complex myeloablative conditioning programme,[163, 174] and can be associated with side effects such as vomiting, hair loss, organ damage and risk of infertility.[237] Chemotherapy and serotherapy regimens are intensive and often require close hospital monitoring.[174] With high risks of mortality, adults with APDS may be unwilling to undergo transplant due to concerns about leaving behind dependents, and would generally prefer to have been receiving an alternative treatment to prevent lymphoma (and the subsequent need for HSCT) in the first place.[43]

Sleep disruption is common amongst people who undergo HSCT, with more than 50% experiencing sleep disruption before the transplant and up to 82% reporting sleep disruption during the transplant hospitalisation.[238] Individuals who do undergo HSCT must also spend approximately one month in an isolation room while their immune system rebuilds, which may be emotionally challenging.[239] HSCT can also have long-term psychosocial impacts on individuals with APDS, such as struggling to keep up with school and/or their career, feeling fatigued during

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the first few years post-HSCT and having an increased sense of vulnerability to health issues.[240] Undergoing HSCT also places substantial emotional, physical, financial, and time-related burdens on caregivers, along with associated psychological stress.[241]

Direct cost of current clinical management

The requirement for combinations of therapies in APDS results in compounded direct medical costs and substantial hospital resource use.[3, 6, 12, 13] As the manifestations of APDS are lifelong, so is the need for treatment, resulting in a high, long-term individual patient cost to the NHS. In light of the combined cost of existing treatments for APDS (see Table 4), an effective, targeted treatment that can alleviate APDS manifestations and complications, would substantially reduce healthcare resource use associated with the condition.

Table 4. Direct costs of current clinical management for individuals with APDS

Treatment	Direct costs
Antimicrobials	Despite being less expensive compared to other treatments,[242] antimicrobials are rarely received by individuals with APDS in isolation, nor do they prevent or manage many of the other progressive aspects and symptoms of the disease.[3, 118]
IRT	As IRT only temporarily increases IgG levels, 87–89% of people with APDS eventually receive long-term IRT which accrues high annual costs.[12, 15] Moreover once on IRT, people with APDS are highly unlikely to discontinue treatment as confirmed by four clinicians during follow-up questions in Exercise 3 of the Expert Consultancy.[14] In the UK, IRT use is associated with a high cost, with the total cost of IRT for immunodeficiency between 2015–2016 estimated to cost over £40 million.[243]
Immunosuppressives	In Exercise 4 of the Expert Consultancy, clinicians estimated that amongst individuals with APDS who have been prescribed immunosuppressives (including mTOR inhibitors), the average number of medicated days is 341 per year; immunosuppressives are often required long-term once initiated.[14] As individuals with APDS may be administered a combination of several, concomitant immunosuppressive therapies during the year,[6] this can lead to a high individual patient cost to the NHS. Treatment with mTOR inhibitors is also linked to severe and costly AEs such as pulmonary damage, lymphedema and metabolic disorders, leading to increased resource use from multidisciplinary healthcare specialists.[244]
Surgeries	In Exercise 4 of the Expert Consultancy, clinicians stated that adolescent and adult individuals with APDS are likely to experience a wide range of surgeries, including but not limited to tonsillectomy, bronchoscopy, splenectomy and lobectomy. Please refer to the Expert Consultancy report for further detail.[14] As the cumulative use of these medical procedures and surgical interventions can result in high costs.
HSCT	Based on data from the UKPID registry (25th March 2024) and the cohort in the Dimitrova et al., 2022 cohort, people with APDS may have to undergo multiple transplants and require intense conditioning prior the procedure to increase the likelihood of success.[32, 43] As such, the costs associated with HSCT pre- and post-procedure can be high, especially for individuals:[245-247] • Requiring intense conditioning pre-HSCT, • Experiencing a relapse, • Requiring additional transplant(s), • Needing supplemental treatments such as IRT or for GVHD, or

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	• Requiring chemotherapy as a maintenance therapy post-HSCT for malignancy.

Abbreviations: AE: adverse event; APDS: activated PI3Kδ syndrome; GVHD: graft versus host disease; HSCT: haematopoietic stem cell transplant; IgG: immunoglobulin G; IRT: immunoglobulin replacement therapy; mTOR: mammalian target of rapamycin; NHS: National Health Service; UK: United Kingdom.
Source: All About APDS,[118] Coulter et al., 2017,[12] Coulter et al., 2018,[3] Dimitrova et al., 2022,[29] Elkaim et al., 2016,[15] Griffin et al., 2019,[246] Maccari et al., 2018,[6] Maziarz et al., 2018,[245] Pharming Data on File, 2023,[14] Pokharel et al., 2020,[242] Shillitoe et al., 2018,[197] Xuan et al., 2021,[247] Zaza et al., 2013.[244]

Summary of unmet need in APDS

There are currently no licensed treatments available for APDS in the UK. Consequently, individuals receive multiple symptomatic treatments in an attempt to manage individual manifestations, and the combination of immune dysregulation and immune deficiency.[18, 27, 28] Despite current management, individuals with APDS continue to experience disease progression and life-threatening manifestations, resulting in a reduced life expectancy compared with people without APDS.[3, 12, 13, 15, 18]

Additionally, the manifestations and treatments of APDS continue to substantially negatively impact HRQoL and daily living.[4, 11, 23] This highlights a **clear unmet need for a generally well tolerated, licensed disease-modifying treatment that targets the underlying hyperactive PI3Kδ enzyme complex,[167] addressing the range of manifestations leading to improvements in HRQoL and mortality**.

Anticipated positioning of leniolisib in the future treatment pathway

It is well accepted that treatments should aim to address the underlying cause of disease manifestations.[203, 248, 249] Leniolisib is the first targeted therapy for APDS which selectively inhibits the catalytic subunit of the PI3Kδ enzyme complex, addressing the hyperactivity of the enzyme and restoring signalling homeostasis in the PI3Kδ pathway. This targeted mechanism of action allows leniolisib to treat the underlying cause of APDS, improving both the immune dysregulation (e.g. lymphoproliferation) and immune deficiency (e.g. severe, recurrent and/or persistent infections) observed.[9, 17, 27, 33-35] In turn, this leads to improvements in HRQoL, improving an individual's energy levels and ability to complete daily activities, as well restoring their hope and general wellbeing.[17, 26, 35-37]

As a targeted treatment with the potential to prevent the progression of manifestations, irreversible end-organ damage, and spare and/or halt the use of multiple symptomatic treatments, we expect that leniolisib will be prescribed following diagnosis in individuals aged 12 years or older. In Exercise 3 of the Expert Consultancy, clinicians provided their insights on the positioning of leniolisib:

- Leniolisib would be prescribed for all individuals with APDS (regardless of the type),[14]
- At least four of the five clinicians agreed that they would not expect to prescribe certain immunosuppressive treatments alongside leniolisib, in order to avoid over-suppression of the immune system,[14]
- Two clinicians agreed that if HSCT was completely successful, leniolisib would not be used; however, if disease activity remained after HSCT (due to e.g. mixed donor chimerism, graft rejection, or incomplete engraftment), individuals may still receive leniolisib,[14]
- Lastly, in the circumstance that an individual discontinues leniolisib (e.g. due to compliance, adverse effects or to undergo HSCT),[14] it is reasonable to expect that these individuals would revert back to receiving current clinical management, as appropriate.

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Please refer to the Expert Consultancy report for further detail.[14]

B.1.5 Equality considerations

There are several equality issues related to APDS, that NHS England may want to consider. Variable manifestations may make it challenging to accurately recognise and diagnose APDS,[162] leading to delayed diagnoses with a median delay of seven years (reported in the SLR by Jamee et al., 2019).[18, 250] Awareness of APDS in the medical community is still low and can compound diagnostic challenges. People with suspected APDS can be referred to up to six different clinicians during the APDS diagnosis pathway.[251] Misdiagnoses and low awareness of the disease may lead to inconsistency in the clinical management of people with APDS. This issue is not expected to be considered within this submission, but does highlight a consideration for NHS England for the diagnosis and management of people with APDS.

Given that APDS was only recognised as a unique disease in 2013,[2] there are no UK or European clinical guidelines, except for Sweden,[171] for the management of APDS. This may lead to sub-optimal and inconsistent use of off-label medicines and variable polypharmacy approaches to care for individuals with APDS.[3, 12, 17, 27]

Additionally, a suitable donor for HSCT will not always be available, as exemplified by individuals of African descent who are often faced with inequalities in access to HSCT due to having the lowest probability of finding an appropriately matched unrelated donor.[60] Access to HSCT may also be restricted for some young people with APDS due to the lack of parental consent.[61]

B.2 Clinical effectiveness

Summary

Relevant clinical studies for leniolisib in individuals with APDS

- The efficacy and safety of leniolisib for the treatment of individuals with APDS has been explored comprehensively in an international clinical trial programme. This included a successful, placebo-controlled, triple-blinded RCT (Study 2201 Part II) assessing leniolisib for the treatment of APDS versus placebo (in combination with selected symptomatic treatments). Further evidence is provided by a single-arm within-participant, dose-escalation trial, Study 2201 Part I, and an ongoing long-term extension, Study 2201E1.[17, 27, 35, 38]
- Across the clinical trial programme, a total of 38 people received treatment with leniolisib. These trials enrolled adults and adolescent 12 years of age and older [redacted][17, 27, 35] in line with the population defined within the final scope for this evaluation.
- In addition, 72 individuals with APDS have received leniolisib in a real-world setting as part of Pharming's Early Access Programme, including six individuals in the UK across three centres.[29]

Efficacy (Section B.2.6)

- By targeting the underlying cause of APDS, treatment with leniolisib results in rapid B cell normalisation, indicating reconstitution of the immune system:
  - Leniolisib met the **co-primary endpoint** in Study 2201 Part II, producing a **statistically significant increase in naïve B cells as a percentage of total B cells** relative to placebo by Week 12, with a difference in adjusted means of 37.30

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(p=0.0002). An improvement in naïve B cell proportions was maintained throughout Study 2201E1.[17, 35]
    - Alongside naïve B cells, normalisation of B and T cells, immunoglobulin levels and chemokine and cytokine levels were observed across Study 2201 and Study 2201E1, indicating reconstitution of the immune system; in turn, this leads to amelioration of the immune dysregulation (e.g. lymphoproliferation) and immune deficiency (e.g. infections) observed in people with APDS.[17, 27, 35, 38]
- Leniolisib led to rapid improvements for the manifestations associated with immune dysregulation in APDS, including lymphadenopathy and splenomegaly:
    - Leniolisib met the second **co-primary endpoint** in Study 2201 Part II, demonstrating **statistically significant improvements in log10 transformed sum of product diameters (SPD) of index lesions** versus placebo, with a difference in adjusted means of –0.25 (nodal; p=0.0006). Reductions in lymphoproliferation were maintained in Study 2201E1, as demonstrated by responder analyses.[17, 35, 39]
    - Secondary and exploratory endpoints in Study 2201 Part II demonstrated statistically significant reductions in spleen bi-dimensional size (p=0.0148) and spleen organ volume (p=0.002) compared to placebo.[17]
- Participants in the leniolisib trials experienced long-term benefits with leniolisib treatment:
    - Reduction in the rate of infections:
        - In Study 2201E1, a nominally significant decrease in annualised infection rates of 25% was reported with each additional year of leniolisib treatment (−0.282 infections per year, one-sided p=0.0256; DCO: 13th March 2023).[41] Reductions in the incidence of infections were accompanied by sustained reductions in IRT use, as well as some individuals achieving IRT freedom, and no increase in antibiotic usage, throughout Study 2201E1.[17, 35, 38, 41, 42]
    - Findings from the trials demonstrate leniolisib treatment improving cytopenias, suggesting a reduction in autoimmunity.[17, 35, 38]
    - Leniolisib treatment also led to improvements in two out of three participants who experienced gastrointestinal manifestations who were investigated as part of a case study; 2/2 participants remain symptom-free and have discontinued use of other treatments for their gastrointestinal manifestations.[40] In addition, in people with APDS in the EAP presenting with gastrointestinal manifestations prior to initiation of leniolisib, 44% of gastrointestinal manifestations achieved remission.[64]
    - In a case study of six study participants, of the three participants who had developed bronchiectasis prior to entering Study 2201 Part I, bronchiectasis did not progress in any of the individuals through six years of treatment with leniolisib during Study 2201E1, no additional pulmonary support was required, and all three individuals were stable at Year 6 of treatment.[36] Moreover, clinically meaningful improvements or remission of lung disease manifestations were observed in 53% of people with APDS lung disease manifestations receiving leniolisib in the EAP.[64]
    - In Study 2201 Part II, investigator narratives observed an increased tolerance for physical activity and decreased fatigue in 70.0% of participants receiving leniolisib versus 44.4% receiving placebo.[17] Furthermore, 80% of affected individuals with APDS in the EAP had at least clinically meaningful improvements in chronic fatigue, with 27% of affected individuals achieving remission.[64]
    - In Study 2201E1, as of the latest DCO (13th March 2023), a case of classical Hodgkin's lymphoma was reported which led to treatment discontinuation; this AE

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was not considered to be related to leniolisib, by the investigator. No other new malignancies were reported in the clinical trials, including in participants with a history of lymphoma[35] and no participants received HSCT whilst receiving leniolisib treatment.[43]

- The clinical improvements seen with leniolisib treatment have a positive impact on the everyday lives of people with APDS, with numerical improvements in HRQoL measures:[37, 38, 44]
  - Numerical increases from baseline were shown in all SF-36 scales in Study 2201 Part I and Part II, which were maintained throughout Study 2201E1 for leniolisib treatment groups, with CfB and responder analyses demonstrating meaningful long-term changes in general health and physical component summary (PCS) scores.
  - In Study 2201 Part I and Part II, there were numerical improvements in PtGA scores for leniolisib treatment groups, which were maintained throughout Study 2201E1, indicating long-term changes in patient-reported wellbeing and disease activity.

- To supplement findings from the leniolisib clinical trials, real-world evidence from the intra-patient assessment of infections and hospitalisation rates using historical National Institutes of Health data also showed that leniolisib treatment led to reductions in annualised infection (mean difference, pre- vs post-leniolisib treatment initiation: 2.723, [95% CI: 1.001–4.437], p=0.0004) and hospitalisation rates (mean difference, pre- vs post-leniolisib treatment initiation: 0.297, [95% CI: -0.093–0.687], p=0.054).[252]

Safety (Section B.2.10)

- Leniolisib was generally well tolerated by all participants in Study 2201 Part I and Part II, with an overall AE profile comparable to placebo; leniolisib remained generally well tolerated with long-term therapy during Study 2201E1.[17, 27, 35, 38]
  - Across the three leniolisib clinical trials, 82.0% (433/528) AE/TEAEs reported by participants who were administered leniolisib were Grade 1 or Grade 2. In Study 2201 Part II, 19.0% (4/21) of participants in the leniolisib group experienced Grades 3–5 AEs, compared with 50% (5/10) in the placebo group.[17]
- In Study 2201 Part II, when compared to placebo, the leniolisib group reported fewer study-drug related AEs (23.8%, [5/21] for leniolisib versus 30.0%, [3/10]) for placebo group).[17] In Study 2201 and Study 2201E1, none of the AEs/TEAEs reported that led to discontinuation nor the two deaths were determined to be study drug related by investigators.[17, 35, 38]

Conclusion

Overall, clinical evidence demonstrates that leniolisib provides benefit to people with APDS across a range of clinically- and patient-relevant endpoints, whilst being generally well tolerated. Leniolisib targets the underlying pathophysiology of APDS, normalising immune cell subset levels. Improved immune system functioning translates into long-term improvements in both immune dysregulation and immune deficiency, leading to a reduction and cessation in the use of supportive medications, improvements in HRQoL and is expected to substantially reduce mortality.

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B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) and subsequent update were conducted on 11th November 2021 and 18th May 2023 respectively, to identify all relevant clinical evidence on the efficacy and safety of leniolisib or other PI3K inhibitors and current clinical management for the treatment of participants with APDS. The interventions considered within the SLR included leniolisib, antimicrobials (antibiotics, antivirals and antifungals), IRT, immunosuppressive therapies (including steroids), HSCT and surgical interventions (such as tonsillectomy).[3, 12, 13, 18] To ensure all the latest relevant data were captured in the SLR, supplementary targeted searches which focused on studies reporting on leniolisib were conducted on 9th April 2024.

In total, 30 unique studies and 88 case studies were identified by the clinical SLR and targeted searches, of which 10 studies/case studies reported on leniolisib:

- Study 2201 (Part I and Part II): 7 records,
- Study 2201E1: 8 records,
- Seven real-world evidence (RWE) studies reporting on leniolisib.

Full details of the SLR and targeted searches, including the search strategy, study selection process and detailed results are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Of the studies included in the SLR, the efficacy and safety of leniolisib in APDS was primarily investigated in Study 2201 (Part I and Part II) and Study 2201E1. An overview of the three trials is provided in Table 5.[17, 27, 35] These trials enrolled adults and adolescents 12 years of age and older, in line with the target population for this appraisal.

The pivotal Study 2201 Part II (triple-blinded, international RCT) provided direct, clinical evidence for the efficacy and safety of leniolisib versus placebo over a 12-week treatment period, with selected concomitant treatments permitted (Section B.2.3.1).[17]

Study 2201E1 represents the leniolisib trial with the largest sample size in the clinical trial programme (N=37) and the longest expected data collection period of up to six years and three months.[35, 46] In this evidence submission, results are reported from the second (DCO: 13th March 2023) and first (DCO: 13th December 2021) interim analyses of Study 2201E1, which include data available for up to six and five years of leniolisib exposure, respectively.[35, 38]

In addition to the leniolisib clinical trial programme, Pharming have established an Early Access Programme (EAP), to provide leniolisib individuals who were unable to enrol within the clinical trial programme; a total of 72 individuals with APDS have receiving leniolisib, including six individuals with APDS across three centres in the UK.[43] Supportive real-world evidence from the EAP has been presented in this submission.[64]

Table 5. Summary of the leniolisib trials providing clinical effectiveness evidence

Study	Study 2201 Part I [NCT02435173]	Study 2201 Part II [NCT02435173]	Study 2201E1 [NCT02859727]
Study design	Phase II, international, multicentre, open-label, non-randomised, within-participant, dose-finding, dose escalation study	Phase III, triple-blinded, randomised, international, multicentre, placebo-controlled study	Open-label, non-randomised, international, multicentre extension study
	N=6	N=31	N=37

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Eligible Population	Individuals (12–75 years old) with APDS		
Intervention	Leniolisib		
Comparator(s)	None (dose-finding study)	Placebo	None (open-label extension study)
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	No	Yes	Yes
Reported outcomes specified in the decision problem[a]	• Immunophenotype measures (including lymphocyte counts [such as naïve B cells], serum immunoglobulin levels, and cytokine and chemokine levels) • Immune dysregulation measures (including **lymphadenopathy [lymph node size], splenomegaly [spleen volume/size]** and **cytopenias**) • Immune deficiency measures (see next row for specific endpoints) • Lung disease **(bronchiectasis-associated airway disease** and **advanced lung disease)** • Fatigue • **Malignancy (including lymphoma) and mortality[b]** • Disease severity and HRQoL measures (SF-36 and PtGA) • Adverse and serious effects of treatment		
	• Immune deficiency measures (**infection rates** and **rate of antibiotic use**)	• Immune deficiency measures (**infection rates, rate of IRT use** and **rate of antibiotic use**)	• Immune deficiency measures (**infection rates, rate of IRT use** and **rate of antibiotic use**)

Footnotes: [a]Outcomes marked in **bold** represent outcomes considered within the economic modelling. [b]Mortality was not measured as an efficacy endpoint in Study 2201 or Study 2201E1 due to their shorter duration; safety findings related to discontinuation or death are outlined in Section B.2.10.5.
Abbreviations: APDS: activated phosphoinositide 3 kinase delta syndrome; EAP: early access programme; HRQoL: Health-related quality of life; IRT: immunoglobulin replacement therapy; SF-36: 36-item short form survey; PtGA: patient global assessment; WPAI-CIQ: work productivity and activity impairment and classroom impairment questionnaire.
Source: Rao et al., 2017,[27], Rao et al., 2023,[17] Rao et al., 2023,[35], Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis, 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38]

Clinical evidence informing the economic model

As described in Section B.3, the de novo economic model captures the age-dependent profiles of key manifestations observed in individuals with APDS. The model evaluates the effect of leniolisib on the age-specific proportions of individuals experiencing each category of

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manifestation and requiring treatments that manage either specific or multiple manifestations, over a lifetime horizon.[253]

Clinical findings from the leniolisib clinical trials and EAP survey informed how leniolisib would be expected to impact the incidence, resolution and severity of manifestations and treatment use in individuals with APDS. In Study 2201E1, the incidence and prevalence of manifestations and treatment use was measured in individuals with a median leniolisib exposure of 3.0 years (range: 1.2–6.0 years) [DCO: 13th March 2023].[38, 254] Study 2201 Part II and expert insights collected from a group of clinicians in the Expert Consultancy (see Section B.1.3 for further detail) provided additional data informing the model.[14, 17] For details on how available clinical data informed and were applied in the economic model, please refer to Section B.3.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design and methodology

The trial designs and methodology of Study 2201 (Part I and Part II) and Study 2201E1 are summarised in Table 6, with further details provided below.

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Table 6. Summary of trial methodology of the leniolisib clinical trials

	Study 2201 Part I (N=6)	Study 2201 Part II (N=31)	Study 2201E1 (N=37)
Study design	Phase II, international, multicentre, open-label, non-randomised, within-participant, dose-finding, dose escalation study	Phase III, triple-blinded, randomised, international, multicentre, placebo-controlled study	Open-label, non-randomised, international, multicentre extension study
Study locations	Study 2201 Part I and Part II were conducted at ten sites in nine countries: Belarus, the Czech Republic, Germany, Ireland, Italy, the Netherlands, the Russian Federation, the United Kingdom and the USA		Study 2201E1 has been conducted at eight sites in seven countries: Belarus, the Czech Republic, Germany, Italy, the Netherlands, the Russian Federation and the USA[a]
Study duration	12 weeks		Six years and three months[b]
Interventions	Three increasing doses of leniolisib (10 mg, 30 mg, 70 mg bid)	2:1 ratio of leniolisib 70 mg or placebo bid	Leniolisib 70 mg bid
Co-primary endpoints	• Safety parameters including AEs, physical exam, vital signs, ECG, safety laboratory (haematology, blood chemistry, urinalysis) • Dose-PD and PK/PD relationship of leniolisib via single and multiple dose concentrations of leniolisib, and pAkt inhibition in unstimulated and stimulated whole blood	• CfB in % naïve B cells out of total B cells • CfB in the log10 transformed SPD in up to six of the largest lesions from measurable nodal/lymph node index lesions, selected as per the Cheson methodology from MRI or CT imaging	Safety parameters including AEs, physical exam, vital signs, ECG, safety laboratory (haematology, blood chemistry, urinalysis)
Key secondary endpoints	• SF-36, PtGA scores and individual participant narratives	• 3D volume of index and measurable non-index lesions selected as per the Cheson methodology, and 3D volume	• Frequencies of infections and other disease complications[c]

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	Study 2201 Part I (N=6)	Study 2201 Part II (N=31)	Study 2201E1 (N=37)
		and bi-dimensional sizes of spleen • SF-36, PtGA scores and individual participant narratives • Safety parameters including AEs, physical exam, vital signs, ECG, safety laboratory (haematology, blood chemistry, urinalysis)	• SF-36, PtGA scores and individual participant narratives
Pre-planned subgroups	N/A	• Age group: <18 years and ≥18 years • Sex: male and female (added to SAP prior to database lock) • Genetic diagnosis: APDS1 and APDS2 (added to SAP post database lock)	N/A

Footnotes: [a]The study sites in Belarus and the Russian Federation have now been closed, with closing dates of January 2022 and October 2022, respectively. [b]In Study 2201E1, the expected data collection timeframe for the primary endpoint is up to six years and three months whereas the data collection timeframes differ for the various secondary endpoints. [c]Across all the clinical trials, infections were reported as treatment-emergent adverse events and were not associated with concomitant medication administered to participants during the trial period;[37, 38, 43, 44] for further information, please refer to Section B.2.6.3.
Abbreviations: 3D: three-dimensional; AE: adverse events; APDS: activated PI3K delta syndrome; bid: Bis In Die (twice daily); CfB; Change from baseline; CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; pAkt: phosphorylated protein kinase B; PD: pharmacodynamic; PI3K: phosphoinositide 3-kinase; PK: pharmacokinetic; PtGA: patient global assessment; SAP: statistical analysis plan; SD: standard deviation; SF-36: 36-item short form survey; SPD: sum of product of diameters; USA: United States of America; WPAI-CIQ: work productivity and activity impairment plus classroom impairment questionnaire.
Source: Rao et al., 2017,[27], Rao et al., 2023,[17] Rao et al., 2023,[35], Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38]

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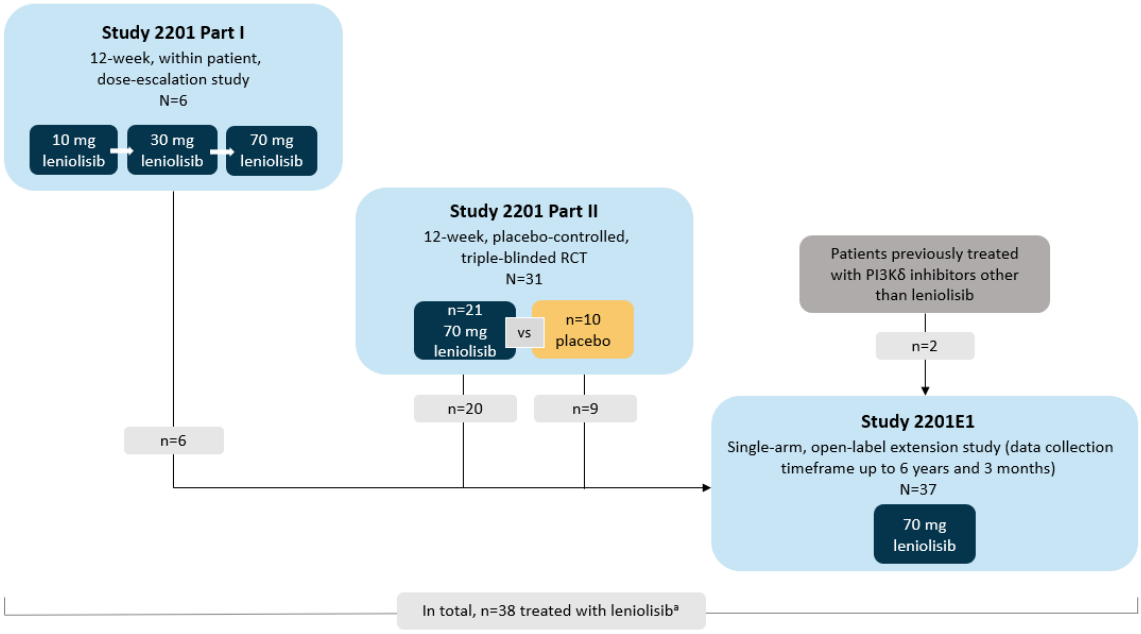
Study designs and duration

As illustrated in Figure 8, Study 2201 Part I assessed the safety and tolerability of orally administered leniolisib at three different dose levels (10 mg, 30 mg and 70 mg bid), before informing the fixed dose of leniolisib 70 mg bid for Study 2201 Part II.[17, 27] Study 2201E1 provided continuation of leniolisib therapy for those who directly enrolled from Study 2201 (Part I and Part II, including participants who had received placebo in Study 2201 Part II) or access to leniolisib therapy for individuals with APDS who previously received treatment with PI3Kδ inhibitors other than leniolisib, such as nemiralisib and seletalisib.[35, 43] Some participants who enrolled in Study 2201E1 had a gap between treatment with leniolisib in Study 2201 and Study 2201E1, as detailed per participant in Appendix N.1.4. Further details regarding the overall design and schedule of key assessments during the treatment period for Study 2201 (Part and Part II) and Study 2201E1 are provided in Appendix N.1.1 and N.1.2.

Figure 8. Overview of Study 2201 and Study 2201E1



Footnotes: All doses were administered bid. [a]n=6 from Part I, n=21 and n=9 from the leniolisib and placebo arms in Part II, respectively, and n=2 participants treated with other PI3Kδ inhibitors.
Abbreviations: bid: Bis In Die (twice daily); mg: milligrams; PI3Kδ: phosphoinositide 3-kinase δ; RCT: randomised controlled trial.
Source: Rao et al., 2017,[27], Rao et al., 2023,[17] and Rao et al., 2023.[35]

Both parts of Study 2201 were comprised of a 12-week treatment period with safety followed up for four weeks after the last day of dosing.[37, 44] At the protocol development stage, it was considered that a study duration of 12 weeks would be sufficiently long to assess the co-primary endpoints in Study 2201 Part II, based on findings in Study 2201 Part I, as well as previous trials which observed reductions in lymphadenopathy within 1–2 months.[44, 255-257] In addition, as restrictions on the use of immunosuppressants were applied during Study 2201 (see 'Concomitant medication' further below), a trial duration of longer than 12 weeks was considered unethical. As discussed in Section B.1.4.3, immunosuppressive therapies are used to treat lymphoproliferation, autoimmunity, as well as enlarged spleen/liver in individuals with APDS. A longer trial would therefore have increased the risk of autoimmune manifestations and lymphoproliferation for participants in the placebo group.

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Study 2201E1 was designed to gather long-term evidence (with the longest expected data collection period of up to six years and three months), and assess the long-term safety and efficacy of leniolisib.[35, 38, 46]

Randomisation, stratification and blinding

Study 2201 Part II was triple-blinded, whereby the participant, investigator and sponsor were all blinded, reducing any potential bias and increasing the validity of the clinical results observed. In consideration of the ultra-rare status of APDS and that there are currently no licensed treatments,[1, 151] participants in Study 2201 Part II were randomised 2:1 to receive leniolisib 70 mg bid or matching placebo in order to maximise the proportion of participants receiving the study drug.[17, 37] Randomisation was not stratified.[37]

Eligibility criteria

Participants were selected according to inclusion and exclusion criteria that were highly consistent across Study 2201 and Study 2201E1. The trial eligibility criteria specified that participants must be between 12–75 years old,[17, 35, 44] which represents the population anticipated to be eligible to receive leniolisib in the UK, in line with the anticipated marketing authorisation, and the population for this appraisal.

All participants were required to have documented APDS-associated pathogenic gene variant in *PI3KCD* (APDS1) or *PIK3R1* (APDS2).[37, 46, 258] This population aligns with UK clinical practice which encounters and treats both individuals with APDS1 or APDS2, and was unanimously confirmed by five clinicians in Exercise 3 of the Expert Consultancy.[14]

An inclusion criterion in Study 2201 (Part I and Part II) specified that participants must present with nodal and/or extranodal lymphoproliferation, and clinical findings and manifestations compatible with APDS such as a history of repeated oto-sinopulmonary infections (includes respiratory infections, as well as infections of the ear, such as otitis media [an infection of the middle ear]) and/or organ dysfunction (e.g. lung, liver). In addition, to facilitate measurement of the lymphoproliferation endpoints, participants must have at least one measurable nodal lesion on a CT or MRI scan.[258] The study population is expected to be well aligned with the population that would receive leniolisib in UK clinical practice as:

- Lymphoproliferation is a hallmark characteristic of APDS, and was observed in 86% of individuals with APDS in the ESID registry cohort (146/170; November 2022 dataset).[13]
- Recurrent respiratory infections and otitis media were highly reported in people with APDS in the ESID registry, 92% (156/170; November 2022 dataset) and 73% (100/138; November 2023 dataset), respectively.[13, 18]
- All five clinicians in Exercise 3 of the Expert Consultancy agreed that most individuals with APDS they see would present with at least one measurable lymph node lesion (on CT or MRI scans), hence highlighting that the trial populations are generalisable to UK clinical practice.[14]

An exclusion criterion in the leniolisib clinical trials specified that individuals with any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardise the participant in the study, were not eligible to participate.[255, 259] As such, no participants included in the leniolisib clinical trials had a medical history of HSCT.[43] Individuals undergo complex myeloablative conditioning regimens, such as chemotherapy or serotherapy, to prepare the body for HSCT which may have confounded study results (if individuals who had received HSCT were eligible to enter the trials).[174] Additionally,

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HSCT is associated with poor outcomes and adverse complications in APDS.[20, 32, 233] In Exercise 3 of the Expert Consultancy two clinicians agreed that if HSCT was completely successful, leniolisib would not be used; however, if disease activity remained after HSCT (due to e.g. mixed donor chimerism, graft rejection, or incomplete engraftment), individuals may still receive leniolisib.[14] As people with remaining disease activity post-HSCT would have a similar disease profile to the trial participants, the exclusion of people who had undergone HSCT from the trials is not expected to affect generalisability of the results. Additionally, benefit has been demonstrated with leniolisib treatment in one individual in clinical practice who experienced unsuccessful HSCT.[260]

The full eligibility criteria for Study 2201 and Study 2201E1 are described in Appendix N.1.3.[37, 38, 44]

Concomitant medication

Within the leniolisib clinical trial programme, all trial participants were allowed to continue receiving selected concomitant treatments, including: steroids (except glucocorticoids above 10 mg or 25 mg prednisone or equivalent per day within 2 weeks for Study 2201 Part I or Study 2201 Part II/Study 2201E1, respectively), antimicrobials, IRT, anilides (analgesics such as paracetamol),[261] propionic acid derivatives (e.g. non-steroidal anti-inflammatory drugs such as ibuprofen) and selective beta-2-adrenoreceptor agonists.[37, 38] This generally aligns with current practice in the UK, where symptomatic treatments for people with APDS can include but is not limited to antimicrobials, IRT and immunosuppressive therapies (see Section B.1.4.3).

Immunosuppressive co-medication may increase the susceptibility of people with APDS to infections.[188, 255] Therefore, previous or concurrent use of some classes of immunosuppressive medications (such as mTOR inhibitors, rituximab and cyclophosphamide) was prohibited within the leniolisib clinical trials, if administered during the study or within a certain timeframe prior to first dosing of leniolisib or placebo (Table 7).[37, 38, 44]

It is acknowledged that mTOR inhibitors and rituximab are considered part of current clinical management for people with APDS in the UK (see Section B.1.4.3). However, in Exercise 3 of the Expert Consultancy, at least four of the five clinicians agreed they would not prescribe each of sirolimus (loading and maintenance doses), rituximab, mycophenolate mofetil or cyclosporin alongside a PI3Kδ inhibitor;[14] therefore, the concomitant medication in the clinical trials is generally reflective of how leniolisib would be used in clinical practice. Externally controlled indirect matched comparisons of the effectiveness of leniolisib versus current clinical management in the UK (including immunosuppressive therapies, informed by real-world European data) are provided in Section B.2.6 and in Appendix N.2.2, to validate results of Study 2201 Part II.[262]

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Table 7. Examples of prohibited immunosuppressive co-medication in the leniolisib clinical trials

Examples of prohibited immunosuppressive co-medications[a]	Time frame within which co-medication was not permitted
• Belimumab • Cyclophosphamide	• Not permitted within six months prior to first dosing of the study medication
• B cell depleting medication (e.g., rituximab)	• Not permitted within six months prior to first dosing of the study medication • If previously received, absolute B lymphocyte counts in the blood must have regained normal values
• Cyclosporine A • Mycophenolate • 6-mercaptopurine • Azathioprine • Methotrexate	• Not permitted within three months prior to first dosing of the study medication
• mTOR inhibitors (e.g. sirolimus, everolimus) • Non-selective PI3K inhibitors • Selective PI3Kδ inhibitors	• Not permitted within six weeks prior to first dosing of the study medication • Short-term use for up to a total of five days was allowed but only up to one month prior to enrolment in the study
• Glucocorticoids above 10 or 25 mg prednisone or equivalent per day (Study 2201 Part I and Study 2201 Part II/Study 2201E1, respectively)	• Not permitted within two weeks prior to first dosing of the study medication

Footnotes: [a]Other immunosuppressive medications where the effects were expected to persist at start of dosing of the study medication were also prohibited.
Abbreviations: mTOR: mammalian target of rapamycin; PI3K: phosphoinositide-3 kinase.
Source: Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38]

For further information regarding concomitant medication that was prohibited during the trials, please do refer to the respective CSRs.[37, 38, 44]

Endpoints

The leniolisib clinical trials (Study 2201 and Study 2201E1) investigated clinically and patient-relevant endpoints, across a wide range of APDS-related manifestations and clinical markers of disease;[17, 27, 35] see Section B.2.4.2 for details on the measurement of endpoints and statistical analyses performed.

The co-primary endpoints for Study 2201 Part II were primarily selected for their clinical relevance, as well as their feasibility to be measured within the 12-week study duration. Lymphoproliferation and immune cell imbalances, such as the arrested development of B cells

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(and subsequent immune dysregulation and immune deficiency) are hallmark clinical manifestations of APDS (see Section B.2.4.2 for further information regarding how these endpoints were measured).

B.2.3.2 Baseline characteristics

Patient numbers

Fewer than 100 individuals with APDS had been reported upon within the literature at the time of Study 2201 Part I;[44] subsequently, a SLR conducted by Jamee et al. in 2019 identified 243 individuals within the literature.[18] Considering that APDS is a recently described ultra-rare IEI,[1, 151] and that low numbers of individuals with APDS are reported upon within the literature, a relatively large number individuals (N=39) were enrolled across Study 2201 and Study 2201E1.[17, 27, 35]

Baseline demographic characteristics

A summary of the baseline demographic characteristics across the enrolled populations of Study 2201 and Study 2201E1 can be found in Table 8.

Baseline demographic characteristics were consistent between the trials and representative of the wider APDS population. Age and sex across the trials were reflective of those published in observational studies of APDS.[17, 18, 27, 35] The study centre locations for Study 2201 and Study 2201E1 span across seven European countries, the United States of America and the Russian Federation,[37, 38, 44] all of which are anticipated to have similar demographics to the UK population. All five clinicians in Exercise 3 of the Expert Consultancy agreed that baseline characteristics in Study 2201 Part II were generalisable to individuals with APDS they see in routine clinical practice.[14]

Sex, ethnicity and weight were comparable across the leniolisib and placebo arms of Study 2201 Part II. The difference in age of participants between treatment groups in Study 2201 Part II is most likely due to the small sample size.[17] The difference is not likely to have biased results, because:

- The proportions of participants under the age of 18 years in each treatment arm were similar,[17] indicating well balanced age groups
- As Thalhammer et al., 2021 reported in an analysis of the ESID registry, more than 90% of individuals had already experienced a disease manifestation as early as the age of 6–10 years.[114] Therefore, it is highly likely that participants in both treatment arms will have experienced similar levels of disease progression by study entry

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Table 8. Baseline demographic characteristics for participants included in Study 2201 and Study 2201E1 (safety analysis set)

	Part I (N=6)	Part II (N=31)			Study 2201E1 (Interim Analysis) (N=37)
		Placebo (n=10)	Leniolisib 70 mg bid (n=21)	Total population (N=31)	
Total participants that completed the study – n	6	10	21	31	37 enrolled in study[a] (ongoing)
Age (years) – mean (SD)	22.2 (5.64)	26.7 (13.43)	22.2 (10.00)	23.7 (11.19)	22.7 (9.96)
Participants under 18 – n (%)	2[b] (33.3)	4 (40.0)	8 (38.1)	12 (38.7)	NR
Sex – n (%)					
Male	4 (66.7)	4 (40.0)	11 (52.4)	15 (48.4)	21 (56.8)
Female	2 (33.3)	6 (60.0)	10 (47.6)	16 (51.6)	16 (43.2)
Predominant Race – n (%)					
White	6 (100.0)	7 (70.0)	18 (85.7)	25 (80.6)	31 (83.8)
Asian		1 (10.0)	1 (4.8)	2 (6.5)	2 (5.4)
Black (or African American for Study 2201E1)		1 (10.0)	1 (4.8)	2 (6.5)	2 (5.4)
Other		1 (10.0)	1 (4.8)	2 (6.5)	2 (5.4)
Ethnicity – n (%)					
Hispanic or Latino	1 (16.7)	1 (10.0)	0	1 (3.2)	3 (8.1)
Not Hispanic or Latino	3 (50.0)	7 (70.0)	14 (66.7)	21 (67.7)	22 (59.5)
NR	2 (33.3)	2 (20.0)	7 (33.3)	9 (29.0)	12 (32.4)
Weight (kg) – mean (SD)	63.92 (7.625)	68.55 (11.661)	66.14 (15.550)	66.92 (14.259)	65.88 (12.28)
Height (cm) – mean (SD)	170.63 (9.676)	166.19 (8.153)	163.15 (8.248)	164.13 (8.208)	165.27 (8.90)
BMI (kg/m^2) – mean (SD)	22.10 (3.463)	24.89 (4.345)	24.76 (5.121)	24.80 (4.811)	24.154 (4.37)

Footnotes: [a]A total of 6/37 participants (16.2%) discontinued from the study; the reason for discontinuation from the study was death, adverse event, physician decision, participant/guardian decision (all n=1) and study terminated by sponsor (n=2). The individual who discontinued due to physician decision had completed six years of follow-up in Study 2201E1, and after discontinuation has continued to receive leniolisib via the EAP. The two Russian participants who discontinued due to study termination by sponsor have also continued to receive leniolisib via the EAP.[43] Study 2201E1 is expected to be completed in January 2027.[43] [b]One male participant (17 years of age) and one female participant (16 years of age) at the time of enrolment.
Abbreviations: APDS: activated phosphoinositide 3 kinase delta syndrome; bid: Bis In Die (twice daily); BMI: body mass index; NR: not reported; SD: standard deviation.
Source: Rao et al., 2017,[27], Rao et al., 2023,[17] Rao et al., 2023,[35], Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38]

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Baseline clinical characteristics

Baseline clinical characteristics for Study 2201 and Study 2201E1 are provided in Table 9.

Baseline clinical characteristics, including prior manifestations, were similar across the three trials and generally in line with the those seen in the wider APDS population.[17, 18, 27, 35, 38] The proportions of participants with APDS2 were 19.4% in Study 2201 Part II and 18.9% in Study 2201E1, in line with the SLR report by Jamee et al., 2019 in which 26.3% of the APDS population have APDS2.[18, 38]

In Study 2201 Part II, the majority of manifestations were comparable across the treatment groups, with history of bronchiectasis and gastrointestinal complications being more prevalent in the placebo group.[17] The limited sample size may have impacted the balance of prior conditions between the randomised treatment arms and these manifestations were only recorded if reported by investigators, and may not have been recorded consistently.[43] However, the expected impact of this difference on trial outcomes and their validity is low as the overall clinical profile of participants was similar between the treatment groups.[17] Furthermore, in Exercise 3 of the Expert Consultancy, three clinicians agreed that these differences in clinical baseline characteristics would not be anticipated to confound the outcomes assessed in the trial. For further detail on the responses provided by clinicians, please refer to the Expert Consultancy report.[14]

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Table 9. Summary of medical history by system organ class in Study 2201 and Study 2201E1 (safety analysis set)

	Part I (N=6)	Part II (N=31)			Study 2201E1 (Interim Analysis) (N=37)
		Placebo (n=10)	Leniolisib 70 mg bid (n=21)	Total population (N=31)	
Total participants that completed the study – n	6	10	21	31	37 enrolled in study[a] (ongoing)
Disease type – n (%)	APDS1, 6 (100.0)	APDS1, 9 (90.0) APDS2, 1 (10.0)	APDS1, 16 (76.2) APDS2, 5 (23.8)	APDS1, 25 (80.6) APDS2, 6 (19.4)	APDS1, 30 (81.1) APDS2, 7 (18.9)
Lung function (respiratory, thoracic and mediastinal disorders) – n (%)	4 (66.7)	9 (90.0)	14 (66.7)	23 (74.2)	27 (73.0)
Bronchiectasis	3 (50.0)	8 (80.0)	8 (38.1)	16 (51.6)	17 (44.7)
Asthma	2 (33.3)	4 (40.0)	7 (33.3)	11 (35.5)	10 (27.0)
Interstitial lung disease	0 (0.0)	2 (20.0)	3 (14.3)	5 (16.1)	5 (13.5)
Lung disorder	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Restrictive pulmonary disease	1 (16.7)	1 (10.0)	1 (4.8)	2 (6.5)	3 (8.1)
Small airways disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Obstructive airways disorder	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.2)	1 (2.7)
Infections and infestations – n (%)	6 (100.0)	9 (90.0)	20 (95.2)	29 (93.5)	36 (97.3)
Respiratory tract infection	2 (33.3)	1 (10.0)	2 (9.5)	3 (9.7)	3 (8.1)
Sinusitis	3 (50.0)	4 (40.0)	12 (57.1)	16 (51.6)	18 (48.6)
Pneumonia	3 (50.0)	6 (60.0)	9 (42.9)	15 (48.3)	18 (48.6)
Cytomegalovirus infection	1 (16.7)	1 (10.0)	1 (4.8)	2 (6.5)	3 (8.1)
Epstein-Barr virus infection	3 (50.0)	1 (10.0)	1 (4.8)	2 (6.5)	4 (10.5)

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	Part I (N=6)	Part II (N=31)			Study 2201E1 (Interim Analysis) (N=37)
		Placebo (n=10)	Leniolisib 70 mg bid (n=21)	Total population (N=31)	
Herpes simplex	1 (16.7)	1 (10.0)	0 (0.0)	1 (3.2)	2 (5.3)
Herpes zoster	0 (0.0)	0 (0.0)	1 (4.8)	1 (3.2)	1 (2.6)
Otitis media	1 (16.7)	4 (40.0)	6 (28.6)	10 (32.3)	14 (37.8)
Blood and lymphatic system disorders – n (%)	5 (83.3)	7 (70.0)	15 (71.4)	22 (71.0)	28 (75.7)
Lymphadenopathy	6 (100.0)	10 (100.0)[b]	21 (100.0)[b]	31 (100.0)[b]	23 (62.2)
Cytopenias	NR	5 (50.0)	13 (61.9)	18 (58.1)	NR
Anaemia	1 (16.7)	2 (20.0)	4 (19.0)	6 (19.4)	8 (21.6)
Lymphopenia	1 (16.7)	3 (30.0)	6 (28.6)	9 (29.0)	10 (27.0)
Neutropenia	2 (33.3)	0 (0.0)	3 (14.3)	3 (9.7)	5 (13.5)
Thrombocytopenia	2 (33.3)	2 (20.0)	1 (4.8)	3 (9.7)	6 (16.2)
Splenomegaly	6 (100.0)	3 (30.0)	7 (33.3)	10 (32.3)	13 (35.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) – n (%)	4 (66.7)	6 (60.0)	5 (23.8)	11 (35.5)	16 (43.2)
Diffuse large B-cell lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Lymphoproliferative disorder	0 (0.0)	2 (20.0)	3 (14.3)	5 (16.1)	6 (16.2)
Non-Hodgkin's lymphoma	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders – n (%)	3 (50.0)	7 (70.0)	10 (47.6)	17 (54.8)	25 (67.6)
Surgical and medical procedures – n (%)	3 (50.0)	9 (90.0)	17 (81.0)	26 (83.9)	29 (78.4)

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	Part I (N=6)	Part II (N=31)			Study 2201E1 (Interim Analysis) (N=37)
		Placebo (n=10)	Leniolisib 70 mg bid (n=21)	Total population (N=31)	
Tonsillectomy	2 (33.3)	7 (70.0)	6 (28.6)	13 (41.9)	14 (37.8)
Lung lobectomy	0 (0.0)	1 (10.0)	1 (4.8)	2 (6.5)	3 (8.1)
Ear tube insertion	3 (50.0)	4 (40.0)	3 (14.3)	7 (22.6)	10 (27.0)

Footnotes: [a]A total of 6/37 participants (16.2%) discontinued from the study; the reason for discontinuation from the study was death, adverse event, physician decision, participant/guardian decision (all n=1) and study terminated by sponsor (n=2). The individual who discontinued due to physician decision had completed six years of follow-up in Study 2201E1, and after discontinuation has continued to receive leniolisib via the EAP. The two Russian participants who discontinued due to study termination by sponsor have also continued to receive leniolisib via the EAP.[43] Study 2201E1 is expected to be completed in January 2027.[43] [b]Whilst all participants in Study 2201 Part II were required to have lymphadenopathy for trial inclusion, documented clinical history of lymphoproliferation (e.g. lymphadenopathy, splenomegaly, hepatomegaly) varied.
Abbreviations: APDS: activated phosphoinositide 3 kinase delta syndrome; bid: Bis In Die (twice daily); NR: not reported.
Source: Rao et al., 2017,[27], Rao et al., 2023,[17] Rao et al., 2023,[35], Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38]

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Baseline medication use

Medication use at baseline of Study 2201 and Study 2201E1 is provided in Table 10. Baseline medication use was generally similar across Study 2201 and Study 2201E1, and was representative of published estimates of treatment use in the wider APDS population (see Section B.1.4.3).[17, 27, 35, 38]

Within Study 2201 Part II, both baseline glucocorticoid and antibiotic use were balanced between treatment arms, although previous sirolimus treatment was more common in the placebo group (30.0%) compared to the leniolisib group (19.0%).[17] As with other differences between treatment groups, this is likely due to the small trial sample size and is expected to have a minimal impact on the validity of results.

Table 10. Participant baseline medication use in Study 2201 and Study 2201E1 (Safety analysis set)

	Study Part I (N=6)	Study Part II (N=31)			Study 2201E1 (Interim Analysis) (N=37)
		Placebo (n=10)	Leniolisib 70 mg bid (n=21)	Total population (N=31)	
Total participants that completed the study – n	6	10	21	31	37 enrolled in study[a] (ongoing)
Baseline glucocorticoids – n (%)					N/A
No	4 (40.0)	4 (40.0)	9 (42.9)	13 (41.9)	
Yes	6 (60.0)	6 (60.0)	12 (57.1)	18 (58.1)	
Baseline IRT – n (%)					
No	1 (17.0)	3 (30.0)	7 (33.3)	10 (32.3)	10 (27.0)
Yes	5 (83.0)	7 (70.0)	14 (66.7)	21 (67.7)	27 (73.0)
Baseline antibiotic prophylaxis – n (%)					
No	3 (50.0)	4 (40.0)	10 (47.6)	14 (45.2)	15 (40.5)
Yes	3 (50.0)	6 (60.0)	11 (52.4)	17 (54.8)	22 (59.5)
Previous sirolimus treatment[b] – n (%)					
No	5 (83.0)	7 (70.0)	17 (81.0)	24 (77.4)	37 (100.0)
Yes	1 (17.0)	3 (30.0)	4 (19.0)	7 (22.6)	0 (0.0)

Footnotes: [a]A total of 6/37 participants (16.2%) discontinued from the study; the reason for discontinuation from the study was death, adverse event, physician decision, participant/guardian decision (all n=1) and study terminated by sponsor (n=2). The individual who discontinued due to physician decision had completed six years of follow-up in Study 2201E1, and after discontinuation has continued to receive leniolisib via the EAP. The two Russian participants who discontinued due to study termination by sponsor have also continued to receive leniolisib via the EAP.[43] Study 2201E1 is expected to be completed in H2 2024.[b]Sirolimus was not permitted within six weeks prior to first dosing of the study medication. Short-term use for up to a total of five days was

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allowed but only up to one month prior to enrolment in the study.
Abbreviations: APDS: activated phosphoinositide 3 kinase delta syndrome; bid: Bis In Die (twice daily); IRT: immunoglobulin replacement therapy; N/A: not available; NR: not reported.
Source: Pharming Data on File, 2024,[263] Rao et al., 2017,[27], Rao et al., 2023,[17] Rao et al., 2023,[35], Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 14.1-6.1).[38]

B.2.3.3 Concomitant medication use

During both Study 2201 and Study 2201E1, nearly all participants received concomitant medication alongside leniolisib or placebo (see Appendix N.1.5).[35, 37, 38, 44] The range of medications prescribed across Study 2201 and Study 2201E1 and small numbers of participants receiving each specific treatment reflects the current manifestation-led, individualised nature of treatment use in the real-world.

Concomitant use of steroids and IRT were covariates in the statistical analysis for Study 2201 Part II, so any imbalances in use of these medications between treatment arms is unlikely to have biased results.[17] During the trial, antibiotics were more commonly taken in the placebo group (80.0%) than in the leniolisib group (42.9%),[37] as such, a greater clinical benefit may have been provided by antibiotics in the placebo group than in the leniolisib group, providing a conservative estimate of leniolisib treatment effect.

B.2.3.4 EAP survey

A survey of physicians in the leniolisib EAP was undertaken in October 2023. A questionnaire was developed to characterise clinically important changes across a number of body systems affected in individuals with APDS, specifically lymphoproliferation, infections (including those leading to hospitalisations), cytopenia, chronic fatigue, gastrointestinal manifestations, and pulmonary manifestations. As part of the questionnaire, physicians were asked to provide the duration of leniolisib treatment, prior treatments, signs and symptoms present at the start of leniolisib treatment and the current status of those signs and symptoms following leniolisib treatment, with response categories including remission (complete response), meaningful improvement, no change, worsening or new incidence of the manifestations. This questionnaire design allowed assessment of clinically meaningful response to leniolisib in each of the domains relevant to the individuals being treated with leniolisib (as opposed to numerical changes were there is not always an accepted threshold of meaningful response). All data presented were summarised descriptively, and no calculations relating to statistical significance were undertaken.[64]

Thirty physicians were surveyed, of whom 21 (75%) responded. These 21 physicians completed questionnaires for 30 (75%) individuals, from a possible total of 40 individuals from the EAP (at the time of the survey).[64]

Access to leniolisib under the EAP was granted on the basis of lack of available treatment options for the individual patient; therefore, the findings of the EAP survey are unlikely to be due to concomitant current clinical management, nor by chance, but rather due to a real treatment effect of leniolisib.[64]

The duration of leniolisib treatment was as follows; it is highly unlikely that all individuals entering the EAP with overt manifestations would have improved at a specific timepoint only after receiving leniolisib treatment, so the benefit of leniolisib may be underestimated in this survey.[64]

- 0–6 months: 8 individuals
- 6-12 months: 8 individuals

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- 12–24 months: 4 individuals
- >24 months: 10 individuals

Given that the majority of individuals in the EAP were from Europe and the Russian Federation at the time of the survey, it is expected that the findings from the EAP are generablisable to clinical practice in the UK.[43] Please refer to the EAP survey report for further information.[64]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Study group definitions

The analysis sets used in the analysis of Study 2201 and Study 2201E1 are presented in Table 11. No protocol deviations occurred that required data set exclusion in Study 2201 Part I or Study 2201E1, therefore all participants were included in each of the analysis sets. In Study 2201 Part II, four participants were excluded from the PK and/or PD analysis sets due to protocol deviations. Please refer to the respective CSRs for further detail regarding the protocol deviations and Appendix N.1.6 for the baseline characteristics for the primary analysis sets.[37]

Table 11. Trial population used for the analysis of outcomes in Study 2201 and Study 2201E1

Population	Study 2201		Study 2201E1
	Part I	Part II	
Safety	All participants who received any study drug.		
	N=6 (100.0%)	n=31 (96.9%)[a]	N=37[b] (100.0%)
Pharmacokinetic (PK)	All participants with at least one available valid[c] PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.		
	N=6 (100.0%)	n=19 (90.5%)[d]	N=37 (100.0%)
Pharmacodynamic (PD)	All participants with any available PD data who received any study drug and experienced no protocol deviations with relevant impact on PD data. In Study 2201 Part II, for the analysis of the primary co-endpoint, CfB in the percentage of naïve B cells out of total B cells, only participants with <48% naïve B cells at baseline were included (B-PD data set). A supportive analysis using the full PD analysis set was provided.		
	N=6 (100.0%)	n=27 (84.4%)	N=37 (100.0%)

Footnotes: [a]The total population of Study 2201 Part II is n=32 including one screen failure participant; 31 participants were randomised in a 2:1 ratio to leniolisib or placebo. [b]Study 2201E1 initially started with 37 participants enrolled, of which one passed away before the DCO of 13th December 2021. [c]A PK measurement that was not flagged for exclusion was considered a valid measurement. [d]Participants in the placebo group (n=10) were not included in the PK analysis set.
Abbreviations: DCO: data cut-off; PD: pharmacodynamic; PK: pharmacokinetic.
Source: Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023[38] and van Gent et al., 2009.[264]

B.2.4.2 Statistical analyses

Efficacy outcomes (Study 2201 and Study 2201E1)

A summary of the statistical analyses used to evaluate the co-primary efficacy endpoints in Study 2201 Part II can be found in Table 12. Of note, a primary efficacy endpoint was not assessed in

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Study 2201E1, and details regarding the statistical analysis of the primary efficacy endpoint for Study 2201 Part I can be found in the respective CSR.[44, 46] A summary of the statistical analyses used to evaluate the secondary efficacy endpoints is presented in Appendix N.1.7.

A supplementary modified 5-round Delphi panel with 24 clinicians with experience in managing individuals with APDS or PID in Europe or the US was conducted between March and November 2023. This study was conducted building on the RAND/UCLA Appropriateness Method, an internationally recognised technique for using a panel of experts to reach consensus on health practices or policy.[265] Clinicians were eligible to participate on the Delphi panel if they (i) were currently treating ≥ 1 APDS patient, (ii) had previous experience treating ≥ 1 APDS patient or (iii) were currently treating ≥ 1 patient with PID. The Delphi panel first aimed to gather consensus on treatment outcomes that are important in determining how well a new treatment is working in APDS. The final outcomes with consensus were lymphoproliferation (including lymph node size and spleen volume), naïve B-cell count and cytopenia (including haemoglobin levels, platelet count and lymphocyte count). For these outcomes, consensus was then gathered on the amount of improvement in that "you would consider clinically meaningful" or "the smallest improvement on each outcome that you would consider to be meaningful or important". The distribution of Likert scale responses was calculated for each treatment outcome. Consensus was defined prior to data collection as ≥75% of panellists responding "Agree" or "Strongly agree" that an outcome variable would be considered. The modified Delphi panel study can therefore be considered to provide robust thresholds for clinically meaningful treatment response on outcomes that are important for people with APDS. Therefore, the clinically meaningful thresholds agreed on during the Delphi panel study were used in post hoc analyses of data from Study 2201 and Study 2201E1 to determine the proportion of responders to leniolisib treatment for the manifestations agreed to be important in APDS. Please see the report for further details.[266]

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Table 12. Summary of the statistical analyses for primary efficacy outcomes in Study 2201 Part II

Trial	Outcome	Endpoint	Primary Analysis Set	Normal or Clinically Meaningful Changes	Hypothesis Test	Sample Size Calculation	Missing Data
Study 2201 Part II	To assess immunophenotype normalisation with leniolisib in participants with APDS after 12 weeks of leniolisib treatment.	CfB in % of naïve B cells out of total B cells. For further detail on how participant samples were collected for this endpoint, please refer to the respective CSR.	**B-PD analysis set**: participants with a reduced % of naïve B cells at baseline (defined as <48%) were included. To focus this endpoint on participants with a reduced % of naïve B cells at baseline, a threshold of 48% was selected based on the lowest value in a normal reference range.	The normal % of naïve B cells ranges from 48–84% of total B cells. After three months of treatment, a change of ≥20% from baseline in the percentage of naïve B cells out of total B cells in adults or adolescents with APDS, was considered clinically meaningful by clinicians in the modified Delphi study described above.[266]	ANCOVA of the B-PD analysis set[a] (2-sided comparison with a 5% type I error) The model adjusted for baseline naïve B cell frequencies and included categorical (Yes/No) fixed effects for the use of glucocorticoids and IRT at baseline.	With the following assumptions: • 10% of participants were to be excluded from the analysis due to no reduction in naïve B cells at baseline, • A CfB to 12 weeks in the percentage of naïve B cells of 25%, • Comparable variability to Study 2201 Part I (SD=14) A sample size of 27 participants would have provided 98% power to detect a statistically significant difference (overall 5% type I error).	Baseline naïve B cell values were calculated as the arithmetic mean of baseline (Day −1) and Day 1 values; if either value was missing, the existing value was applied. No missing data was imputed.

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				Post hoc analyses were conducted to examine clinically meaningful changes in naïve B cells in participants.			
	To assess lymphadenopathy with leniolisib in participants with APDS after 12 weeks of leniolisib treatment.	CfB in the log10 transformed SPD of up to six of the largest index lesions (nodal), selected as per the Cheson criteria (at baseline) from MRI or CT imaging. For further detail on how the index lesions were imaged, please refer to the respective CSR.	**PD analysis set**, except for one participant whose Baseline index lesion was fully resolved by Day 85 and so log10 SPD could not be derived.	After three months of treatment, a change of ≥20% (in adults with APDS) or ≥25% (in adolescents with APDS) from baseline index lesion SPD, was considered clinically meaningful by clinicians in the modified Delphi study described above.[266] Post hoc analyses were conducted to examine clinically meaningful changes in index lesion SPD in participants.	ANCOVA of the PD analysis set[b] (2-sided comparison with a 5% type I error). The model was adjusted to exclude participants in the PD analysis set with zero lesions at baseline, applied treatments as a fixed effect and log10 transformed baseline SPD as a covariate. Additionally, the model included categorical (Yes/No) covariates for the use of glucocorticoids and IRT at baseline.	Assuming comparable variability of the change from baseline of in the log10 transformed SPD of index lesions to Study 2201 Part I (SD=0.14), with 30 participants, results would have 97% power to detect a statistically significant difference in the change from baseline of the SPD of up to six of the largest index lesions, with an overall 5% type I error.	No missing data was imputed, as the analysis only required baseline and end of study treatments from participants.

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	By requiring both co-primary endpoints to be statistically significant for a positive study, multiple comparisons were controlled tacitly.[17] For Study 2201 Part II, a sample size of 30 was estimated to provide sufficient power (at least 78%) to achieve statistically significant p-values in both co-primary endpoints.[37]

Footnotes: [a]For primary analysis, the B-PD analysis set only included participants with <48% of naïve B cells at baseline. [b]For primary analysis, the PD analysis set excluded participants with zero lesions at baseline.
Abbreviations: ANCOVA: analysis of covariance; APDS: activated PI3K delta syndrome; CfB: change from baseline; CSR: clinical study report; CT: computed tomography; IgG: immunoglobulin G; MRI: magnetic resonance imaging; PD: pharmacodynamic; PK: pharmacokinetic; SPD: sum product of diameters.
Source: NDA Multidisciplinary Review and Evaluation of Leniolisib, 2018,[267] Rao et al., 2023,[17] Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023[38] and van Gent et al., 2009.[264]

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Safety outcomes (Study 2201 and Study 2201E1)

Across both parts of Study 2201 and Study 2201E1, comprehensive safety assessments were completed. In Study 2201 Part I and Study 2201E1, safety was assessed as a primary endpoint, whereas in Study 2201 Part II, the RCT, safety parameters were evaluated as secondary endpoints.[17, 27, 35] Please refer to the respective CSRs for further information regarding the safety reporting procedures and the pre-specified definitions for an adverse event and SAE.[37, 38, 44]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of Study 2201 Part II was performed using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations from NICE), and is provided in Table 13.[268] Randomisation and blinding were adequate, and baseline characteristics were generally well balanced between the treatment arms. Overall, Study 2201 Part II is considered to be of high quality with a low risk of bias.

Quality assessments of Study 2201 Part I and Study 2201E1 were performed using an adapted version of the Critical Appraisal Skills Programme (CASP) checklist (also per recommendations from NICE), and are provided in Table 14. Exposures and outcomes were accurately measured to minimise bias, baseline characteristics were well reported, and follow-up of participants was complete. Overall, both trials were considered to be of high quality with a low risk of bias.

Table 13. Quality assessment results for Study 2201 Part II

Study 2201 Part II	
Was randomisation carried out appropriately?	
Yes/no/unclear	Yes
Justification	Randomisation numbers were assigned in an ascending, sequential order to eligible participants. The investigator entered the randomisation number on the case report form (CRF). A randomisation list was produced using a validated system that automated the randomisation assignment of treatment arms to randomisation numbers in the specified ratio. This procedure ensured that treatment assignment was unbiased.
Was the concealment of treatment allocation adequate?	
Yes/no/unclear	Yes
Justification	Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone involved in the study, with the following exceptions: data monitoring committee (DMC) members, unblinded pharmacist or authorised designee at site, unblinded monitor (where used) and the PK bioanalyst. This procedure ensured that treatment allocation was concealed.
Were the groups similar at outset of the study in terms of prognostic factors?	
Yes/no/unclear	Yes
Justification	Baseline demographic and clinical characteristics were generally well balanced between the leniolisib and placebo groups. As is common in ultra-rare diseases where trials have small sample sizes, some differences in baseline clinical characteristics between the treatment groups were identified (specifically for history of

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Study 2201 Part II	
	bronchiectasis and gastrointestinal manifestations) and have been discussed further in Section B.2.3.2.
Were the care providers, participants and outcome assessors blind to treatment allocation?	
Yes/no/unclear	Yes
Justification	Study 2201 Part II was a triple-blinded study: the participants, investigator staff, sponsor persons performing the assessments and data analysts remained blinded to the identity of study treatments. Study drugs were identical in packaging, labelling, schedule of administration, appearance and odour.
Were there any unexpected imbalances in dropouts between groups?	
Yes/no/unclear	No
Justification	No participants withdrew or discontinued treatment prematurely in Study 2201 Part II.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	
Yes/no/unclear	No
Justification	There was no evidence to suggest the authors measured more outcomes than they reported. Conclusions from investigator narratives are drawn, and clearly labelled. Post hoc analyses were conducted on data collected as part of the pre-specified outcomes, and were clearly labelled.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
Yes/no/unclear	No
Justification	All 31 participants who were randomised to treatment were included in the safety analysis set. For the efficacy analyses, an intention-to-treat analysis was not conducted. The PD analysis set consisted of all participants with any available PD data who received any study drug and experienced no protocol deviations with relevant impact on PD data. However, this is unlikely to have introduced bias into the study results: • The first principle of the intention-to-treat analysis is to analyse participants in the intervention groups to which they were randomised, regardless of the interventions they actually received. In Study 2201 Part II, all participants received the intervention to which they were randomised, so this principle is fulfilled by the PD analysis set, and there should be no risk of bias with respect to deviations from intended interventions. • As described in Section B.2.4.1, four participants were excluded from the PD analysis set due to protocol deviations. Three of these were reported as deviations from inclusion criteria, i.e. participants were actually ineligible for inclusion in the trial, rather than representing post-randomisation exclusions of eligible participants. Therefore, these exclusions should not introduce bias into the results. • The deviations from inclusion criteria occurred in line with the 2:1 treatment allocation ratio (leniolisib: n=2; placebo:

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Study 2201 Part II	
	n=1), so the benefit of randomisation is likely to have been maintained despite these exclusions. • Only one participant excluded from the PD analysis set was eligible for the trial. Therefore, overall, the impact of not conducting an intention-to-treat analysis is expected to be insignificant. Supportive analyses including participants with protocol deviations support results of the main analyses.

Abbreviations: CRF: case report form; DMC: data monitoring committee; PD: pharmacodynamic; PK: pharmacokinetic.
Source: Rao et al., 2023,[17] Study 2201 Part II CSR Version 2.0, Novartis 2022,[37], Study 2201 Protocol and Protocol Amendments, Novartis 2014.[255]

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Table 14. Quality assessment results for Study 2201 Part I and Study 2201E1

	Study 2201 Part I	Study 2201E1
Was the cohort recruited in an acceptable way?		
Yes/no/unclear	Yes	Yes
Justification	Participant selection was established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria was stored with the source documentation at the study site. As described in Section B.2.3.2, the trial population was representative of the wider APDS population.	Participants were enrolled from Study 2201; additionally, participants who were treated previously with PI3Kδ inhibitors other than leniolisib could be enrolled if they met the eligibility criteria at the screening visit. As described in Section B.2.3.2, the trial population was representative of the wider APDS population.
Was the exposure accurately measured to minimise bias?		
Yes/no/unclear	Yes	Yes
Justification	All participants received leniolisib. Exposure to leniolisib was reported.	
Was the outcome accurately measured to minimise bias?		
Yes/no/unclear	Yes	Yes
Justification	Commonly used outcome measures were included. Outcome assessments were performed according to a pre-specified visit schedule for all participants. Outcome measures were objective and were performed according to standardised procedures to minimise bias and variability in assessments. The trial was not blinded, but outcome measures were objective.	
Have the authors identified all important confounding factors?		
Yes/no/unclear	Yes	Yes
Justification	Comprehensive baseline characteristics were measured, including demographic and clinical characteristics and prior concomitant medication.	
Have the authors taken account of the confounding factors in the design and/or analysis?		
Yes/no/unclear	Yes	Yes
Justification	Baseline demographic and clinical characteristics are reported in detail, by age group and participant. As confirmed by expert consultants, differences in baseline characteristics are expected to have minimal impact on the results. Due to the small sample size, no subgroup analyses were performed.	Baseline demographic and clinical characteristics are reported in detail. Subgroup analyses were performed for participants with prior exposure to leniolisib and placebo, as this may have confounded the results.
Was the follow-up of participants complete?		
Yes/no/unclear	Yes	No – study ongoing
Justification	All participants completed the trial.	Long-term data from Study 2201E1 (longest expected data collection period of up to six years and three months) is ongoing.[a]
How precise (for example, in terms of confidence interval and p values) are the results?		
Yes/no/unclear	Yes, the results are considered precise.	Yes, the results are considered precise.

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	Study 2201 Part I	Study 2201E1
Justification	Patient-level results and measures of variability are provided.	Measures of variability (e.g. confidence intervals and p values) are provided. Despite the small sample size, Study 2201E1 observed meaningful within-patient results, some of which reached statistical significance.

Footnotes: [a]In Study 2201E1, the expected data collection timeframe for the primary endpoint is up to six years and three months whereas the data collection timeframes differ for the various secondary endpoints.
Abbreviations: APDS: activated PI3Kδ syndrome; PI3Kδ: phosphoinositide 3-kinase delta.
Source: Rao et al., 2017,[27], Rao et al., 2023,[17], Study 2201 Part I CSR, Novartis 2017,[44] Study 2201 Protocol and Protocol Amendments, Novartis 2014,[255] Study 2201E1 CSR (IA2), Pharming Data on File, 2023[38] and Study 2201E1 Protocol and Protocol Amendments, Novartis, 2016.[259]

B.2.6 Clinical effectiveness results of the relevant studies

In this section, efficacy results for primary, secondary and exploratory endpoints from Study 2201 and Study 2201E1 trial are presented, in line with the relevant outcomes for this appraisal.[17, 27, 35, 38] Table 15 details how the outcomes have been grouped, with links provided to corresponding results sections, and a top line summary of the clinical trial results.

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Table 15. Summarised clinical findings from the leniolisib clinical trials

Section	Outcome(s) and associated manifestation(s)	Clinical trial finding and real-world evidence
B.2.6.1	**Immunophenotype measures**	• Leniolisib met the co-primary endpoint of Study 2201 Part II, **with a statistically significant increase from baseline to Week 12 (Day 85) in naïve B cells as a percentage of total B cells** in participants with fewer than 48% naïve B cells out of total B cells at baseline (p=0.0002). An improvement in naïve B cell proportions was maintained throughout Study 2201E1. • Alongside naïve B cells, normalisation of B and T cells, immunoglobulin levels and chemokine and cytokine levels were observed across Study 2201 and Study 2201E1, indicating reconstitution of the immune system; in turn, this leads to amelioration of the immune dysregulation (e.g. lymphoproliferation) and immune deficiency (e.g. infections) observed in people with APDS.
B.2.6.2	**Immune dysregulation measures**	
	Lymphoproliferation and splenomegaly	Leniolisib met the second co-primary endpoint for lymphadenopathy (CfB in the log10 transformed SPD of the index lesions) in Study 2201 Part II (nodal; p=0.0006). Reductions in both spleen volume and size were observed across the leniolisib clinical trials.
	Cytopenias (autoimmune manifestations; including anaemia and thrombocytopenia)	Cytopenias resolved in a higher percentage of participants receiving leniolisib versus those receiving placebo. A low incidence of cytopenia AEs were reported in Study 2201E1.
	Gastrointestinal manifestations	Leniolisib treatment led to improvements in 2/3 participants who experienced gastrointestinal manifestations who were investigated as part of a case study. Of the two participants that experienced gut-associated lymphoproliferative disorders, both remain symptom-free and have discontinued use of other treatments for their gastrointestinal manifestations.
B.2.6.3	**Immune deficiency measures**	
	Rate of infections	• A nominally significant decrease in annualised infections rates of 25% was reported with each additional year of leniolisib treatment (−0.282 infections per year, one-sided p=0.0256; DCO: 13th March 2023). • Reductions in the incidence of infections were accompanied by sustained reductions in IRT use, as well as some individuals achieving IRT freedom, and no increase in antibiotic usage, throughout Study 2201E1.
B.2.6.4	**Lung disease**	In a case study of six study participants, of the three participants who had developed bronchiectasis prior to entering Study 2201 Part I, bronchiectasis did not progress in any of the individuals through six years of treatment with leniolisib during Study 2201E1, no additional pulmonary support was required, and all three individuals were stable at Year 6 of treatment.
B.2.6.5	**Fatigue**	In Study 2201 Part II, investigator narratives demonstrated an increased tolerance for physical activity/decreased fatigue in 70.0% of participants receiving leniolisib versus 44.4% receiving placebo.
B.2.6.6	**Malignancy and mortality**	Across the three leniolisib clinical trials, there have been no reports of clinically significant, new malignant neoplasms associated with leniolisib.
B.2.6.7	**Disease severity and health-related quality of life**	• Numerical increases from baseline were shown in all SF-36 scales in Study 2201 Part I and Part II, which were maintained throughout Study 2201E1 for leniolisib treatment groups, with CfB and responder analyses

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		demonstrating meaningful long-term changes in general health and physical component summary (PCS) scores. • In Study 2201 Part I and Part II, there were numerical improvements in PtGA scores for leniolisib treatment groups, which were maintained throughout Study 2201E1, indicating long-term changes in patient-reported wellbeing.

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B.2.6.1 Immunophenotype measures

Normalisation of B cell counts and immunoglobulin levels

Increases in the proportion of naïve B cells as a % of total B cells – co-primary endpoint (Study 2201 Part II)

Leniolisib met the co-primary endpoint of Study 2201 Part II, **with a statistically significant increase from baseline to Week 12 (Day 85) in naïve B cells as a percentage of total B cells** in participants with fewer than 48% naïve B cells out of total B cells at baseline, i.e. the B-PD analysis set (see Section B.2.4.1; difference in adjusted means: 37.30, SE: 5.74, [95% CI: 24.06, 50.54], p=0.0002; Table 16, Figure 9).[17, 37] Baseline characteristics for the B-PD analysis set are reported in Appendix N.1.6, and were similar to baseline characteristics of the full trial population.

In Study 2201 Part I, a substantial increase in naïve B cell frequencies as a proportion of total B cells was also observed at the end of the leniolisib 70 mg bid treatment period (i.e. Week 12 of the trial), with a mean absolute CfB of 41.97%.[38] Further supportive analyses supplemented the conclusions drawn from the primary endpoint; see Appendix N 2.1 for additional details.

Table 16. Change from baseline at Day 85 (Week 12) in naïve B cells as a % of total B cells (Study 2201 Part II)

	Adjusted mean CfB (SE)[c]	Comparison of adjusted means			
		Difference	SE	95% CI	2-sided p-value
Primary efficacy analysis (B-PD analysis set)[a]					
Leniolisib 70 mg bid (n=8)	37.39 (5.35)	37.30	5.74	24.06, 50.54	0.0002
Placebo (n=5)	0.09 (6.66)				
Supportive analysis (PD analysis set)[b]					
Leniolisib 70 mg bid (n=13)	34.70 (5.66)	27.94	6.09	15.02, 40.85	0.0003
Placebo (n=8)	6.76 (5.67)				

Footnotes: [a]Only included participants in the PD analysis set with fewer than 48% naïve B cells out of total B cells at baseline. [b]Included all participants in the PD analysis set apart from six participants, for the following reasons: one participant did not have a baseline measurement of total B cells; one had no naïve B cells at baseline and did not have post-baseline naïve B cell assessments; and four had naïve B cell percentages of less than 48% at baseline but no assessment was performed at Day 85. [c]Data were analysed using an ANCOVA model with treatment as a fixed effect and baseline characteristics as a covariate. The use of glucocorticoids and concomitant immune replacement therapy at baseline were both included as categorical (Yes/No) covariates. Baseline was defined as the arithmetic mean of the baseline and Day 1 values when both were available, and if either baseline or the Day 1 value were missing, the existing value was used.
Abbreviations: bid**:** Bis In Die (twice daily); CfB: change from baseline; CI: confidence interval; PD: pharmacodynamics; SE: standard error.
Source: Rao et al., 2023,[17] Study 2201 Part II CSR Version 2.0, Novartis 2022 (Tables 14.2-3.1.1b_ad and 14.2-3.2.1b_ad).[37]

The **improvements in levels of naïve B cells with leniolisib treatment in Study 2201 Part II were rapid** with significant improvements from baseline versus placebo observed as early as Day 29, i.e. the first efficacy assessment timepoint after Day 1. These improvements were maintained across the 12-week study period. Participants treated with leniolisib had significantly greater increases in proportions of naïve B cells out of total B cells versus placebo, at Days 29, 57 and 85.[37] As shown in Figure 9, with leniolisib treatment, the level of naïve B cells reached the

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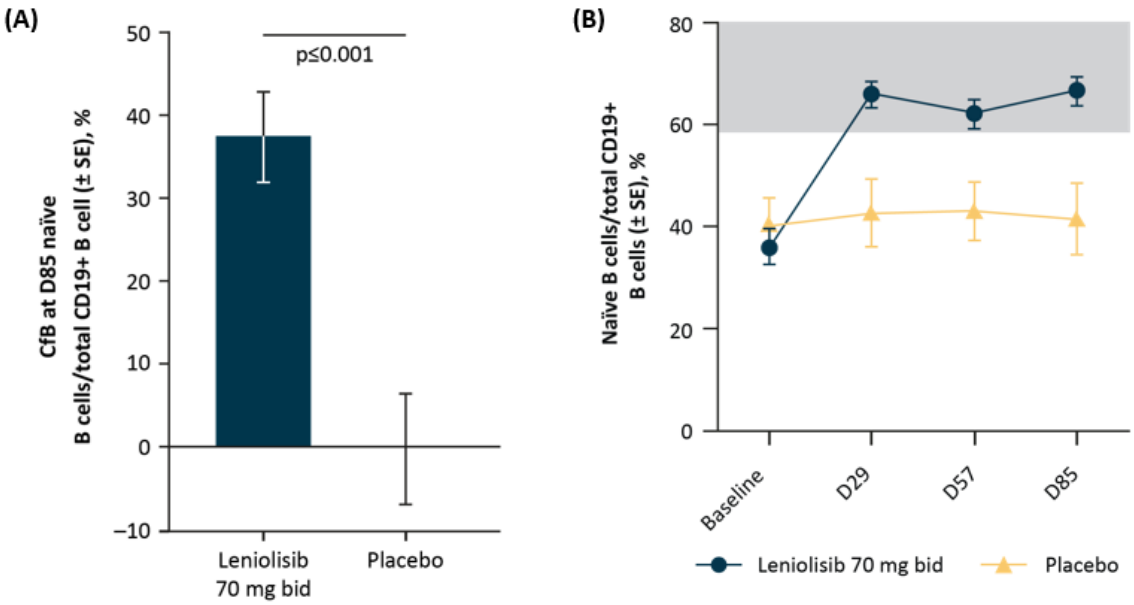
normal reference range defined by European cohort studies by Day 29 and was maintained in this range to Week 12.[17, 264, 269]

Figure 9. Co-primary endpoint in the percentage of naïve B cells out of total B cells, for leniolisib versus placebo groups (Study 2201 Part II; [A] B-PD analysis set; [B] safety analysis set)



Footnotes: (A) Primary naïve B cell endpoint: least square mean of the CfB at Day 85 in the percentage of naïve B cells out of total B cells (CD19+): n values are leniolisib, 8; placebo, 5. Error bars are SE. (B) Comparison of mean positive CfB in the percentage of naïve B cells out of total B cells (CD19+). n values for baseline, Day 29, Day 57 and Day 85 for each group are as follows: leniolisib, 20, 19, 19, 16; placebo, 10, 9, 9, 10. Grey area represents normal reference range for proportion of naïve B cells out of total B cells based on Van Gent et al., 2009 and Morbach et al., 2010.[264, 269]
Abbreviations: CfB: change from baseline; D: Day; SE: standard error.
Source: Rao et al., 2023 (Figure 2 and Figure 4A).[17]

The supplementary Delphi panel with 24 clinicians with experience in managing individuals with APDS or PID, described in Section B.2.4.2, estimated that after three months of treatment, an increase of ≥20% from baseline in the percentage of naïve B cells out of total B cells in adults and adolescents with APDS, would be considered clinically meaningful.[266] By Week 12 (Day 85) of Study 2201 Part II, all participants in the B-PD analysis set treated with leniolisib (12/12) (versus 0% with placebo [0/5]) achieved a ≥20% increase in the percentage of naïve B cells out of total B cells (difference in proportions: 1.00, [95% CI: 0.48, 1.00], p<0.001),[39] indicating that the normalisation in B cell development and maturation with leniolisib treatment is clinically meaningful (Table 17).

Table 17. Responder analysis of participants with ≥20% increase from baseline to day 85 in the percentage of naive to total B cells (Study 2201 Part II; PD analysis set)

	Leniolisib (n=21)	Placebo (n=10)
Participants with <48% naive to total B cells at baseline		
Responder analysis of participants with ≥20% increase from baseline to day 85 in the percentage of naive to total B cells		
Number of participants contributing to the analysis	12	5

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Number of responders (%)	12 (100%)	0 (0%)
RD (95% CI)	1.00 (0.48, 1.00)	
P value[a]	p<0.001	
All participants		
Responder analysis of participants with ≥20% increase from baseline to day 85 in the percentage of naive to total B cells		
Number of participants contributing to the analysis	17	8
Number of responders (%)	16 (94%)	1 (13%)
RD (95% CI)	0.82 (0.42, 0.97)	
P value[a]	p<0.001	

Footnote: Participants without a defined baseline value have been excluded. For participants without data at Day 85, the closest visit day prior to Day 85 is used. [a]Data were analysed using the Fisher's Exact Test.
Abbreviations: CI: confidence interval; RD: risk difference.
Source: Pharming Data on File, 2024.[39]

Long-term effects

Improvement in naïve B cells continued with longer-term treatment beyond Week 12, indicating that **leniolisib is able to sustain immunophenotype normalisation**:

- At baseline in Study 2201E1, the mean (SD) naïve B cell count was 58.16% (20.92; n=5). The mean (SD) CfB for all OLE study participants combined showed that the percentage of naïve B cells increased at each timepoint throughout the OLE, with mean (SD) increase from baseline of 23.58% (16.177) at Day 84 (n=5) and 32.42% (25.293) at Day 252 (n=5).[38]
- To support the clinical relevance of the surrogate endpoints in the leniolisib clinical trials, correlations were investigated between results of the surrogate endpoints and patient-centred endpoints from Study 2201 Part II and Study 2201E1 (for further detail, please refer to the report).[270] Demonstrating the clinical relevance of the long-term increase in the proportion of naïve B cells, post hoc surrogate explorations result show that:[270]
    - The increased proportion of naïve B cells out of total B cells at Day 252 of Study 2201E1 was found to have a positive, statistically significant association with a lower annualised infection rate (p<0.001, negative binomial modelling); an increase of 1 percentage point in the proportion of naïve B cells was associated with a 2.3% reduction in yearly infection rates. Figure 10A presents a scatter plot of numbers of infections by year together with the fitted model for the mean number of infections plotted on the absolute scale.
    - Patient global assessment (PtGA) scores were positively associated with an increasing proportion of naïve B cells out of total B cells (p=0.006, multiple timepoint analysis; Figure 10B)

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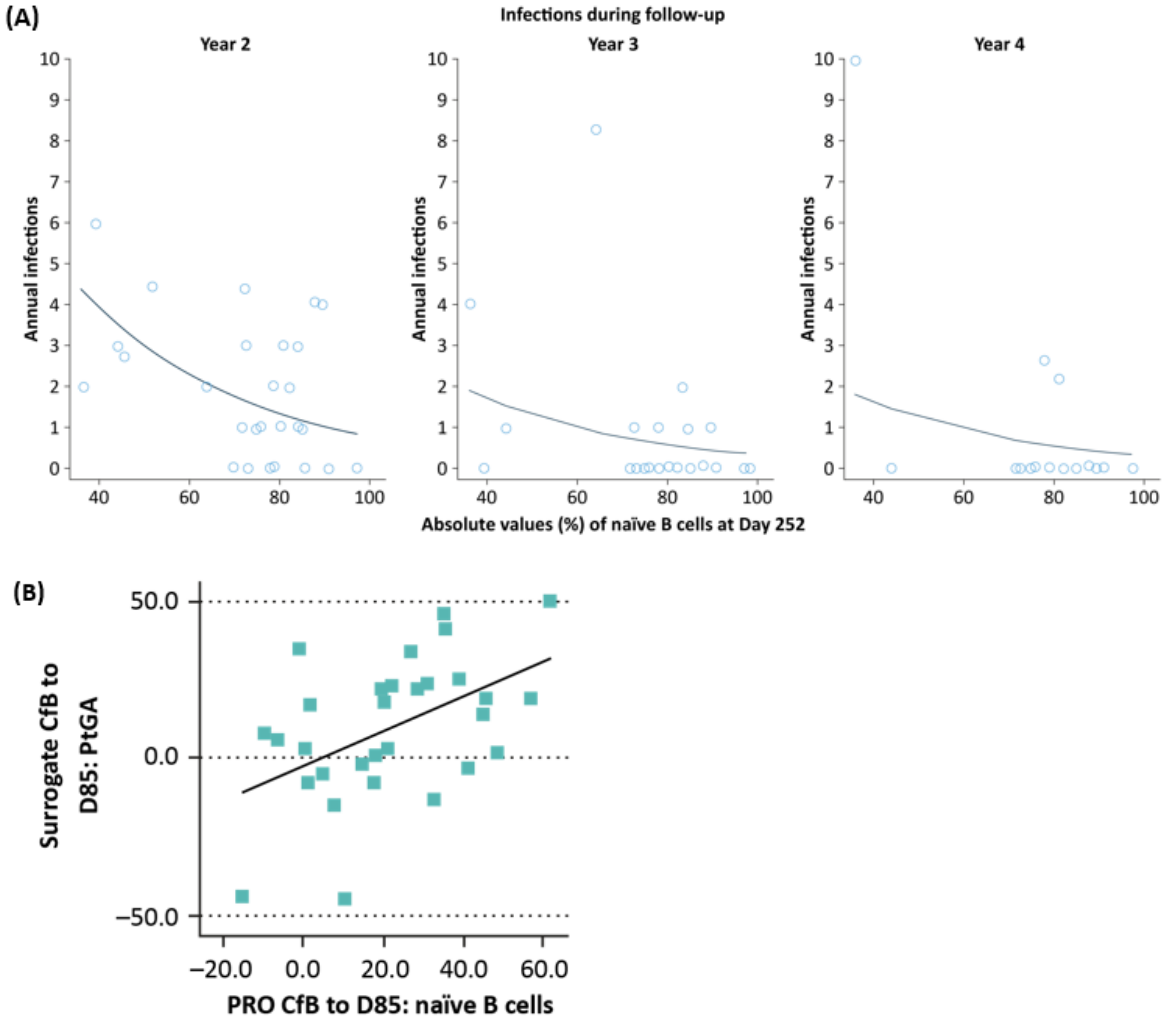
Figure 10. Correlation of percentage of naïve B cells and infections in Study 2201E1, and PtGA in Study 2201 Part II



Footnote: (A) The number of infections for Year 2, 3 and 4 were modelled based on a negative binomial model with the number of infections in Year 1 as a baseline reference value and change from baseline (Study 2201 Part II, study Day 1) to Day 252 in the percentage of naïve B cells as a covariate.
Source: Pharming Data on File, 2024.[270]

Normalisation across other B cell subsets

Given the abnormal development and maturation of B cells associated with APDS (Section B.1.4.2), levels of other B cell subsets were also measured across the leniolisib trials. Results of these other B cell analyses (Appendix N.2.1) are consistent with the co-primary naïve B cell analysis of Study 2201 Part II,[17, 37] and together, **demonstrate normalisation of the B cell development and maturation process and immune system reconstitution**.

Antibody levels

Reductions in IgM levels

In Study 2201 Part II, there were **significantly greater improvements (reductions) in serum IgM levels in participants undergoing leniolisib treatment** compared to those in the placebo arm at Days 29 (p=0.0113), 57 (p=0.0240) and 85 (p=0.0071) [post-hoc analysis].[42] The mean

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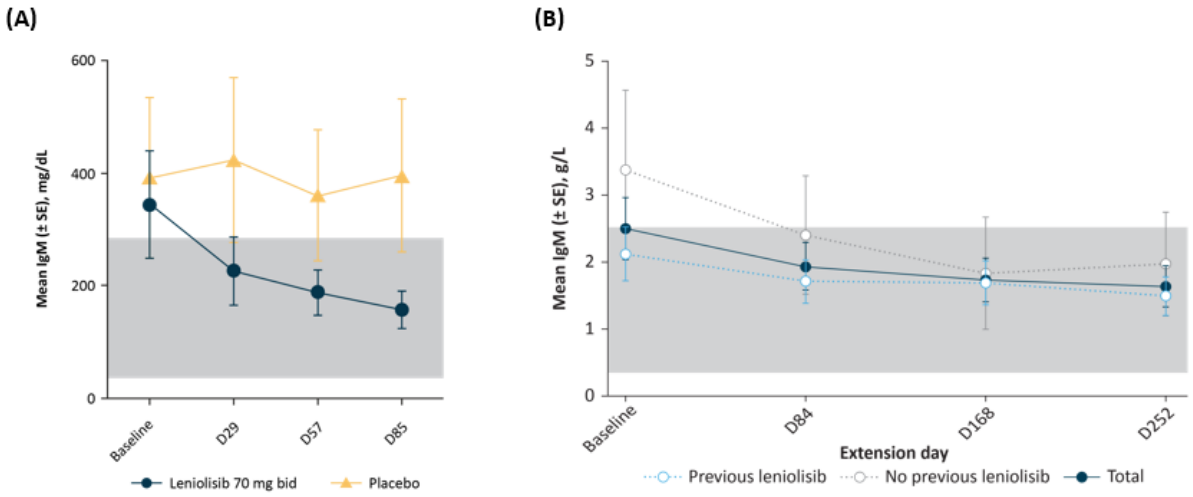
serum IgM level decreased 208.26 mg/dL from baseline to Week 12 (Day 85) in the leniolisib arm but only decreased by 10.00 mg/dL in the placebo arm, as shown in Figure 11.[17] The improvement in IgM levels was sustained in the long-term in Study 2201E1. Mean IgM levels showed a continued decrease from baseline through to Extension Day 252 of Study 2201E1 (see Figure 11); moreover, mean IgM levels were more than 1 g/L below baseline from Week 12 up to Week 36 (Day 252).[38] Reduction in hyper-IgM values associated with APDS may be indicative of the normalisation of the disrupted processes of immunoglobulin class switching, as well as B cell development and maturation.[262] Moreover, the reduction in serum IgM levels observed supports the activity of leniolisib in enabling long-term PI3Kδ signalling normalisation and immune system reconstitution, which in turn is expected to lead to cessation of IRT.

Figure 11. Mean serum IgM levels through Day 85 (Study 2201 Part II; safety analysis set) and Day 252 (Study 2201E1)



Footnote: (A) Mean serum IgM level over time. N values for baseline, Day 29, Day 57, and Day 85 for each group are as follows: leniolisib, 21, 20, 21, and 21; and placebo, 10, 10, 10, and 10. (B) Mean IgM levels over time in Study 2201E1. Extension Day 252 was the last study-defined assessment of serum immunoglobulins. Grey area represents normal reference range for IgM levels based on Van Gent et al., 2009 and Morbach et al., 2010.[264, 269]
Source: Rao et al., 2023 (Figure 4D)[17, 35] and Rao et al., 2023 (Figure 5).[254]

Externally controlled comparison of IgM levels

As described in Section B.2.3, the protocols for the leniolisib clinical trials did not permit recent (near to baseline) or concurrent use of immunosuppressive therapies (including glucocorticoids above 10 mg or 25 mg prednisone or equivalent per day [Study 2201 Part I and Study 2201 Part II/Study 2201E1, respectively], rituximab and mTOR inhibitors – see Section B.2.3.1), and the trials did not include individuals with APDS who had undergone HSCT.[38, 43, 44, 271] Therefore, in the absence of long-term comparative data versus current clinical management for APDS (including immunosuppressive therapies and HSCT), an externally controlled indirect comparison was conducted to validate that the long-term effects of leniolisib on serum IgM levels and on the rate of respiratory infections (see Appendix N2.2) observed in Study 2201E1 are maintained when comparing to current clinical management in people with APDS. Data from Study 2201E1 were compared to an external control sample population enrolled in the ESID registry, the largest registry of individuals with PIDs worldwide.[6, 13, 43, 65, 66]

A summary of the methodology and results of the IgM comparison is provided below, with some further methodological detail in Appendix N.2.2. Inverse probability of treatment weighting was

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used to minimise differences in the baseline characteristics reported for the leniolisib treatment and control groups. In all analyses, data were censored from the first occurrence of: participant withdrawal or death; receipt of HSCT (post-HSCT data were included in sensitivity analyses not censoring for HSCT) or a PI3Kδ inhibitor (control group only) and the end of the observation period. A generalised linear model using complex survey design was used, and bootstrapping using a sampling replacement approach with 1,000 samples was used to calculate confidence intervals.[262] Annualised change in IgM was defined as:[262]

- **Leniolisib treatment group:** The first IgM test recorded during leniolisib treatment as part of one of the clinical trials (Study 2201 Part I and II, or Study 2201E1 for participants who were not part of Study 2201 or were initially assigned to placebo) to the last recorded IgM test.
- **ESID control cohort:** The first IgM test recorded in the ESID registry for individuals with APDS to the second IgM test, divided by time in years between the two tests.

In the base case analysis, participants receiving leniolisib experienced a difference in median annualised change in IgM of -1.09 g/L (95% CI: -1.78, -0.39, p=0.002) versus the control group. The observed trend was consistent when the 95% CI was calculated using the bootstrapping method, resulting in a treatment effect of -1.09 g/L (95% CI: -1.65, -0.53, p=0.001) per year. This result was supported by sensitivity analyses varying the definition of annualised change in IgM in the control arm, as well as when censoring for HSCT was not performed (Appendix N.2.2).[262]

As IgM is known to decrease as a function of age (i.e. IgM levels decrease as age increases),[272] and given the long duration of follow-up for individuals within the ESID registry, relative to participants treated with leniolisib, the results of this post hoc analysis represent a conservative estimate of the treatment effect of leniolisib versus a control population. Despite this, the effect of leniolisib on the annualised reduction of IgM amongst participants with APDS was still statistically significant.[262]

Overall, this externally controlled IgM comparison provides valuable evidence validating the conclusions from Study 2201 Part II and Study 2201E1, that leniolisib treatment is associated with an improvement in IgM levels (representing immunophenotype improvement) compared with current clinical management (including immunosuppressive therapies and HSCT), and that this improvement is sustained in the long term, respectively.[17, 35, 38, 262]

IgG, IgA and IgE levels

Please refer to the respective CSRs for results regarding IgG, IgA and IgE levels in individuals with APDS receiving leniolisib in Study 2201 (Part I and Part II) and Study 2201E1.[37, 38, 44]

Normalisation of T cell counts

Evaluation of T cell immunophenotypes with leniolisib treatment in Study 2201 Part II, as exploratory endpoints, indicated reconstitution of the normal T cell differentiation process:

- A normalisation of the CD4+/CD8+ T cell ratio was seen in Study 2201 Part II, with an increase in the overall percentage of CD4+ T cells and decrease in the percentage of CD8+ T cells (Figure 12). The ratio was calculated to increase from 0.73 to 1.05.[17]
- In Study 2201 Part II, leniolisib increased the percentage of CD8+ naïve T cells,[17] with this trend being maintained through to Week 36 (Day 252) of Study 2201E1 for CD8+ and CD4+ naïve T cells.[35, 38]

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- As shown in Figure 12, levels of senescent (CD57+) and exhausted (PD-1+) CD8+ T cells, as well as exhausted (PD-1+) CD4+ T cells were reduced with leniolisib treatment compared to the placebo group in Study 2201 Part II.[17, 37]
    - These findings were supported by the results from Study 2201 Part I where the frequencies of senescent (CD57+) CD8+ T cells and exhausted (PD-1+) CD4+ T cells also decreased.[27]
- The reduction in exhausted (PD-1+) CD4+ T cell frequencies was sustained in Study 2201E1 up to Week 36 (Day 252) as shown in Figure 12.[38]

Post hoc analyses of the data from Study 2201 (Part I and Part II) and Study 2201E1 found that reduction in the percentage of senescent (CD57+) CD8+ T cell over the 12 week durations of Study 2201 Part I and Part II consistently predicted long-term improvement in PtGA in Study 2201E1 (see Section B.2.6.7). Multivariable analysis found that a 1-point increase in the PtGA scale is independently predicted by a decrease in percentage of senescent CD8+ T cells (–0.77; 95% CI: –1.19 to –0.35; p<0.001).[270] This analysis demonstrates the clinical relevance of the short-term reduction senescent CD8+ T cells, and its predicted associated improvement to HRQoL.

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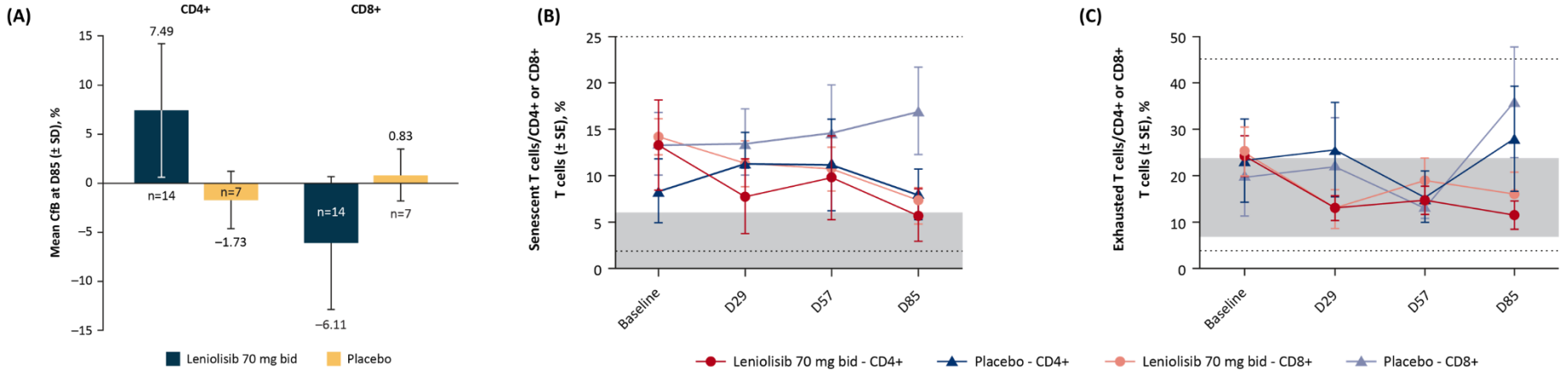
Figure 12. Proportion of total CD4+ and CD8+ T cells, senescent (CD57+) CD4+ and CD8+ T cells, and exhausted (PD-1) CD4+ and CD8+ T cells through Day 85, for leniolisib versus placebo groups (Study 2201 Part II; [A] PD analysis set and [B and C] safety analysis set)



Footnote: (A) Mean CD4+ and CD8+ T cell percentages over time. (B) Mean CD4+ and CD8+ senescent T-cell percentages (CD57+) over time. n values for baseline, Day 29, Day 57, and Day 85 for each group are as follows: leniolisib, CD4+, 18, 15, 16, and 15; placebo, CD4+, 9, 9, 7, and 8; leniolisib, CD8+, 19, 16, 19, and 16; and placebo, CD8+, 10, 9, 7, and 8. (C) Mean CD4+ and CD8+ PD-1+ T-cell percentages over time. n values for baseline, Day 29, Day 57, and Day 85 for each group are as follows: leniolisib, CD4+, 19, 17, 20, and 16; placebo, CD4+, 10, 9, 7, and 8; leniolisib, CD8+, 17, 14, 16, and 16; and placebo, CD8+, 10, 9, 7, and 7. Grey boxes indicate normal ranges for CD4+ cells, and dotted lines indicate normal ranges for CD8+ cells.
Abbreviations: PD: pharmacodynamic; SD: standard deviation; SE: standard error.
Source: Rao et al., 2023 (Table S3, Figure 5A and 5B).[17]

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Normalisation of chemokine and cytokine levels

Please refer to Appendix N.2.1 for results regarding normalisation of chemokine and cytokine levels in individuals with APDS receiving leniolisib in Study 2201 Part II.

B.2.6.2 Improvements in immune dysregulation measures

Reductions in lymphoproliferation and splenomegaly

Reductions in size of index lesions (nodal/lymph node) – co-primary endpoint (Study 2201 Part II)

Reduction in lymphadenopathy was primarily measured as a reduction in index lesion size, defined as the change from baseline in index lesions, assessed by Cheson criteria.[17, 27, 35, 273, 274] This method of assessment has become a standardised measure of response to treatment in non-Hodgkin's lymphoma clinical trials to measure regression of lymphadenopathy.[257, 274, 275] In the leniolisib trials, up to six of the largest lesions from measurable nodal/lymph node were selected using magnetic resonance imaging (MRI) or computerised tomography (CT) imaging.[17, 27, 35, 273, 274] Additional secondary and exploratory endpoints measured the volume and bidimensional size of non-index lesions.[17, 38, 44]

In Study 2201 Part II, leniolisib met the co-primary efficacy endpoint related to lymphoproliferation. **Leniolisib treatment resulted in a statistically significantly decrease in lymphadenopathy**, as measured by the CfB at Week 12 (Day 85) in the log10 transformed sum of product diameters (SPD) of up to six index lesions (nodal) in the PD analysis set, indicating reduced lymphoproliferation (difference in adjusted means: −0.25, SE: 0.06, [95% CI: −0.38, −0.12], p=0.0006; Table 18).[17, 37]

Table 18. Change from baseline at Day 85 in log10 transformed SPD of index lesions (Study 2201 Part II; PD analysis set)

	Mean change (SE)	Comparison of adjusted means			Test versus reference
		Difference	SE	95% CI	2-sided p-value
Primary efficacy analysis (log10 transformed SPD)[a]					
Leniolisib 70 mg bid (n=18)	−0.27 (0.04)	−0.25	0.06	−0.38, −0.12	0.0006
Placebo (n=8)	−0.02 (0.06)				
Supportive analysis (sum of square root of the product of diameters)[b]					
Leniolisib 70 mg bid (n=19)	−23.68 (4.17)	−21.91	6.86	−36.12, −7.69	0.0042
Placebo (n=8)	−1.78 (6.11)				

Footnotes: [a]One participant receiving leniolisib was excluded from the PD analysis set because the baseline index node fully resolved by Day 85, and therefore the "log10 transformed SPD of index lesions" could not be derived. [b]Included all participants from the PD analysis set regardless of the number of lesions at baseline.
Abbreviations: bid: Bis In Die (twice daily); CI: confidence interval; PD: pharmacodynamics; SE: standard error of the mean; SPD: sum of product diameters.
Source: Rao et al., 2023[17] and Study 2201 Part II CSR Version 2.0, Novartis 2022 (Table 14.2-2.4.1b_ad).[37]

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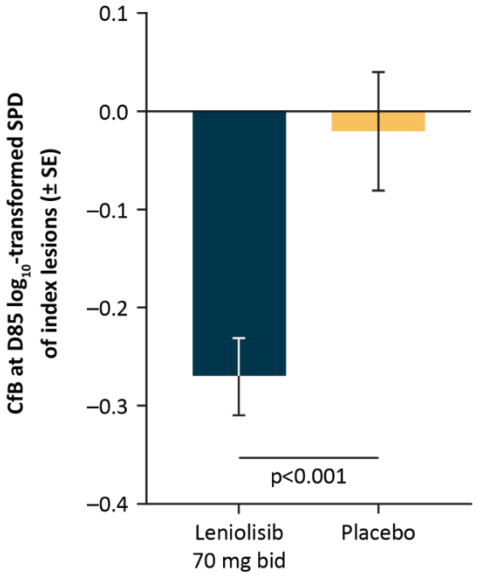
Figure 13. Co-primary endpoint in the log_{10}-transformed SPD of index lesions (co-primary endpoint), for leniolisib versus placebo groups (Study 2201 Part II; PD analysis set)



Footnote: Primary lymphadenopathy endpoint: least square mean of the CfB at Day 85 in the log_{10}-transformed sum of product diameters of the index lymph node lesions in the PD analysis set; leniolisib: n=18; placebo: n=8.
Abbreviation: CfB: change from baseline; PD: pharmacodynamic; SPD: sum of product diameters.
Source: Rao et al., 2022 (Figure 2).[17]

One participant in the leniolisib arm was not included in this analysis at Day 85 as the index lung lesion identified at baseline had fully resolved (reported diameter at Day 85 was zero, so the log10 transformed SPD could not be derived).[17, 37] The effect in the primary analysis was consistent with the supportive analysis which used an alternative method to measure index lesion size (the sum of the square root of the products of diameters of index lesions; difference in adjusted means: −21.91, SE: 6.86, [95% CI: −36.12, −7.69], p=0.0042; Table 18), and across subgroups (Section B.2.7).[37]

In Study 2201E1, **effects of leniolisib treatment on index lesion size were sustained to Day 168/252** (absolute change: –813.00 and percentage change: –49.5% CfB in SPD; n=30) [post hoc analysis].[39]

Post hoc analyses found that a reduction from baseline in SPD in index lesions in Study 2201 Part I and Part II was consistently associated with improvement in SF-36 physical component summary at the chosen timepoints during Study 2201E1 (PCS; see Section B.2.6.7). Single timepoint analysis found that CfB to Day 85 in PtGA was significantly associated with a decrease in the SPD (–1.17; 95% CI: –2.25, –0.09; p=0.034).[270]

Lymphadenopathy: response to treatment

Post hoc analyses of the index lesion size results of Study 2201 Part II were conducted to assess the levels of response to leniolisib. A supplementary Delphi panel with 24 clinicians with experience in managing individuals with APDS or PID estimated that for index lesion SPD, a median reduction of ≥20% in adults and ≥25% in adolescents with APDS after three months of treatment, would be considered clinically meaningful.[266]

The post hoc responder analysis found that a **significantly higher proportion of participants with an enlarged lymph node at baseline treated with leniolisib reached the response**

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threshold for index lesion SPD at Week 12, compared to placebo (risk difference comparing leniolisib and placebo: 0.64, [95% CI: 0.16, 0.89], p=0.002; Table 19).[39]

Table 19. Responder analysis of all participants with an enlarged lymph node at baseline with ≥20 (adults) or 25% (adolescents) reduction from Baseline at Day 85 in index lesion SPD (Study 2201 Part II; PD analysis set)

	Leniolisib (n=21)	Placebo (n=10)
Responder analysis of all participants with an enlarged lymph node at baseline with ≥20% (adults) or ≥25% (adolescents) reduction from Baseline at day 85 in index lesion SPD[a]		
Number of participants contributing to the analysis	19	8
Number of responders (%)	17 (89%)	2 (25%)
RD (95% CI)	0.64 (0.16, 0.89)	
P value[a]	p=0.002	

Footnote: Participants without a defined baseline value were excluded. For participants without data at Day 85, the closest visit day prior to Day 85 was used. [a]Data were analysed using the Fisher's Exact Test.
Abbreviations: CI: confidence interval; RD: risk difference; SPD: sum of product diameters.
Source: Pharming Data on File, 2024.[39]

The Delphi panel with 24 clinicians also estimated that a reduction of ≥30% in index lesion SPD in adults and ≥45% adolescents with APDS, after six months (26 weeks) of leniolisib treatment, would be considered clinically meaningful.[266] By Week 24/36, 24 out of 30 participants (80%) reached the responder threshold (Table 20).

Table 20. Responder analysis of all participants with an enlarged lymph node at baseline with ≥30 (adults) or 45% (adolescents) reduction from baseline at Day 168/252 in index lesion SPD (Study 2201E1; PD analysis set)

		Leniolisib (N=37)
Responder analysis of all participants with an enlarged lymph node at baseline with ≥30% (adults) or ≥45% (adolescents) reduction from Baseline in index lesion SPD[a]		
Day 168/252	Number of participants contributing to the analysis	30
	Number of responders	24
	%	80.0%

Footnote: Participants either had a Day 168 or Day 252 value. [a]Participants without a defined baseline value have been excluded.
Abbreviations: SPD: sum of product diameters.
Source: Pharming Data on File, 2024.[39]

The available evidence shows that leniolisib treatment reduces the incidence of swollen lymph nodes across the body and therefore has the capacity to prevent potentially obstructive thickenings of the mucosal lining in the lung and gut.[11, 12, 23] In Exercise 3 of the Expert Consultancy, four clinicians (4/5) agreed/somewhat agreed that a reduction in lymphoproliferation could be associated with a reduced risk of developing lymphoma (see Section B.2.6.6).[14]

Reductions in splenomegaly

In Study 2201 Part II, changes in the 3D volume and bi-dimensional size of the spleen, was assessed as a secondary endpoint.[17] **Reductions in splenomegaly were reported with leniolisib treatment at Week 12**, as shown in Table 21. In comparison, increases in spleen bi-

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dimensional size were seen in the placebo group, and smaller reductions in spleen organ volume were seen with placebo versus leniolisib.[17, 37] In Exercise 3 of the Expert Consultancy, all five clinicians agreed that long-term changes in lymphadenopathy represent clinically meaningful and patient relevant outcomes within APDS, particularly due to the reduced risk of cytopenia and spleen rupture with reduced splenomegaly.[14]

Table 21. Spleen volume and size changes at Week 12 (Study 2201 Part II; PD analysis set)

Parameter	Mean % CfB at D85 in leniolisib 70 mg bid group (SD) n=19	Mean % CfB at D85 in placebo group (SD) n=8
Spleen organ volume (mm^3)	−26.68 (12.14)	−1.37 (24.24)
Spleen bi-dimensional size (mm^2)	−12.05 (12.75)	+6.22 (21.98)

Abbreviations: bid: Bis In Die (twice daily); CfB: change from baseline; PD: pharmacodynamics; SD: standard deviation.
Source: Study 2201 Part II CSR Version 2.0, Novartis 2022 (Table 14.2-2.7.1b).[37]

Supplementary analyses of Study 2201 Part II demonstrated a statistically significant reduction compared with placebo in spleen organ volume (p=0.0009) and spleen bi-dimensional size (p=0.0079).[37]

A supplementary Delphi panel with 24 clinicians with experience in managing individuals with APDS or PID estimated that for spleen 3D volume, a reduction of ≥25% in adults and ≥27.5% in adolescents with APDS after three months of treatment, would be considered clinically meaningful.[266] A significantly larger proportion of participants in the leniolisib group achieved the responder threshold (risk difference comparing leniolisib and placebo: 0.73, [95% CI: 0.04, 0.93], p=0.018; Table 21).

Table 22. Responder analysis of participants with a ≥25% (adults) and ≥27.5% (adolescents) reduction from baseline at Day 85 in spleen 3D volume in participants with an enlarged spleen at baseline (Study 2201 Part II; PD analysis set)

	Leniolisib (n=21)	Placebo (n=10)
Responder analysis of participants with a ≥25% (adults) and ≥27.5% (adolescents) reduction from baseline at Day 85 in spleen 3D volume in participants with an enlarged spleen at baseline[a]		
Number of participants contributing to the analysis	15	4
Number of responders (%)	11 (73%)	0 (0%)
RD (95% CI)	0.73 (0.04, 0.93)	
P value[a]	p=0.018	

Footnotes: Participants without a defined baseline value have been excluded. For participants without data at Day 85, the closest visit day prior to Day 85 is used. [a]Data were analysed using the Fisher's Exact Test.
Abbreviations: CI: confidence interval; RD: risk difference.
Source: Pharming Data on File, 2024.[39]

In Study 2201 Part II, the observed reduction in lymphoproliferation with leniolisib translated into **statistically significant reductions in spleen bi-dimensional size** (p=0.0148) **and spleen organ volume** (p=0.0020), compared to placebo.[17] Post hoc responder analyses from the Delphi

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panel showed that 67% of participants with an enlarged spleen at baseline reached the response threshold for index lesion SPD at Day 168/252 in Study 2201E1 (Table 23).[39]

Table 23. Responder analysis of participants with a ≥27.5% (adults) and ≥35% (adolescents) reduction from baseline in spleen 3D volume in participants with an enlarged spleen at baseline (Study 2201E1; PD analysis set)

		Leniolisib Total (N=37)
Responder analysis of participants with a ≥27.5% (adults) and ≥35% (adolescents) reduction from baseline in spleen 3D volume in participants with an enlarged spleen at baseline[a]		
Day 168/252	Number of participants contributing to the analysis	24
	Number of responders	16
	%	67.0%

Footnote: Participants either had a Day 168 or Day 252 value. [a]Participants without a defined baseline value have been excluded.
Source: Pharming Data on File, 2024.[39]

Combined reductions in lymphoproliferation and splenomegaly

At the end of Study 2201 Part II, combined responder analyses (post hoc) demonstrate that 100% responders with enlarged lymph nodes and enlarged spleen at baseline achieved a response to leniolisib, as shown in Table **25**, compared to 0% for participants receiving placebo.[276] Through to Week 24/36 of Study 2201E1, 96% of participants responded to leniolisib with enlarged lymph nodes and spleen at baseline (Table 24).[276]

Table 24. Combined responder analysis of participants with reductions from baseline at Day 85 for index lesion SPD and spleen organ volume (Study 2201E1; PD analysis set)

	Leniolisib (n=21)	Placebo (n=10)
Combined responder analysis of participants with reductions from baseline at Day 85[a]		
Number of participants contributing to the analysis	15	4
Number of responders (%)	15 (100%)	0 (0%)
RD (95% CI)	1.00 (0.40, 1.00)	

Footnotes: Participants excluded include those from the PD analysis set without enlarged lymph nodes or enlarged spleen at baseline. For participants without data at Day 85, the closest visit day prior to Day 85 is used. [a]Data were analysed using the Fisher's Exact Test.
Abbreviations: CI: confidence interval; RD: risk difference.
Source: Pharming Data on File, 2024.[276]

Table 25. Combined responder analysis of participants with reductions from baseline at Week 24/36 (Day 168/252) for index lesion SPD and spleen organ volume (Study 2201E1; PD analysis set)

		Leniolisib (N=37)
Combined responder analysis of participants with reductions from baseline at Week 24/36[a]		
Day 168/252	Number of participants contributing to the analysis	24
	Number of responders	23
	%	96.0%

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Footnotes: [a]Participants excluded include those from the PD analysis set without enlarged lymph nodes or enlarged spleen at baseline. Participants either had a Day 168 or Day 252 value. **Abbreviations:** SPD: sum of product diameters.
Source: Pharming Data on File, 2024.[276]

Improvements in cytopenias

Improvements in cytopenias (were measured according to the type of cytopenia (e.g. improvements in anaemia were measured by haemoglobin levels) experienced by participants and recorded as safety data. Levels of haemoglobin, platelets, lymphocytes and neutrophils were all measured during the leniolisib clinical trials.

In Study 2201 Part II, 82% of cytopenias (which included eight reports of anaemia at baseline) improved in the leniolisib arm, whereas 60% of cytopenias improved in participants in the placebo arm (where four participants were reported to have anaemia at baseline).[17] Furthermore, all four cases of thrombocytopenia in participants receiving leniolisib treatment reported at baseline were resolved at Day 85, whereas a participant in the placebo group continued to be affected with thrombocytopenia at Day 85.[17] A case of neutropenia reported at baseline by a participant receiving leniolisib resolved by Day 85 (no participants in the placebo group were affected with neutropenia).[17] Although cytopenia of all causes was measured in the trial, the observed reduction in cytopenias with leniolisib treatment suggests a reduction in autoimmunity.

During Study 2201E1, there was a low incidence of cytopenia AEs overall; when neutropenias occurred, they were found to be transient (neutrophil levels <1000/µL, which returned to >1000/µL at subsequent visits) and did not require treatment.[17, 38] Transient neutropenias did not decrease below an absolute neutrophil count of 500 cells/µL (a clinically significant threshold).[38, 277]

A supplementary modified-Delphi panel with 24 clinicians with experience in managing individuals with APDS or PID reached agreement that a median increase of ≥20% in haemoglobin levels, as well as platelet and lymphocyte counts, after three months of treatment, would be considered clinically meaningful.[266] At Day 85, 83% of participants achieved a response when receiving leniolisib, compared to 50% in the placebo group (risk difference comparing leniolisib and placebo: 0.33, 95% CI: -0.19, 0.81, p=0.245; Table 26).Through to Week 36 (Day 252) of Study 2201E1, 78% of participants achieved a response in the combined responder analyses (see Table 27).[276]

Table 26. Combined responder analysis of participants with reductions from baseline at Day 85 for haemoglobin, platelets and lymphocytes (Study 2201 Part II; PD analysis set)

	Leniolisib (N = 21)	Placebo (N = 10)
Combined responder analysis of participants with increases from Baseline at Day 85 for haemoglobin, platelets and lymphocytes[a]		
Number of participants contributing to the analysis	12	4
Number of responders (%)	10 (83%)	2 (50%)
RD (95% CI)	0.33 (-0.19, 0.81)	
P value[a]	p=0.245	

Footnote: Participants without a defined baseline value have been excluded. For participants without data at Day 85, the closest visit day prior to Day 85 is used. [a]Data were analysed using the Fisher's Exact Test.
Source: Pharming Data on File, 2024.[276]

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Table 27. Combined responder analysis of participants with increases from baseline at Week 36 (Day 252) for haemoglobin, platelets and lymphocytes (Study 2201E1; PD analysis set)

		Leniolisib Total (N=37)
Combined responder analysis of participants with increases from baseline at Day 168/252 for haemoglobin, platelets and lymphocytes[a]		
Day 168/252	Number of participants contributing to the analysis	27
	Number of responders	21
	%	78.0%

Footnote: Participants either had a Day 168 or Day 252 value. [a]Participants without a defined baseline value have been excluded.
Abbreviations: SPD: sum of product diameters.
Source: Pharming Data on File, 2024.[276]

The observed reductions in cytopenia suggest a reduction in autoimmunity with leniolisib treatment, which may lead to increased energy levels, capacity to exercise and perform daily tasks, as well as a reduced risk of bleeding and bruising.[115, 145, 146, 278, 279] For further data regarding the granular levels of cytopenia-related markers, please refer to the CSRs.[37, 38, 44]

Improvements in gastrointestinal manifestations

Changes in gastrointestinal manifestations were examined as part of a case study for three selected participants through chart review as they were not pre-specified endpoints in the leniolisib trials:[40]

- Seven months before Study 2201 Part II, a participant in the placebo group experienced a recurrent *Clostridium difficile* infection and was ultimately treated with faecal transplant 10.5 months into Study 2201E1; despite reports of rectal fistula and proctocolitis, the participant remains stable on leniolisib treatment
- Two other participants experienced gut-associated lymphoproliferative disorders (atypical gut lymphocytic infiltration and lymphoid hyperplasia) before Study 2201 Part II; with leniolisib treatment, both participants remain symptom-free and have discontinued use of other treatments for their gastrointestinal manifestations

These data indicate that gut-associated lymphoproliferative disorders respond to leniolisib treatment, whilst progressive organ dysfunction leading to end-organ damage due to recurrent gastrointestinal infections may require additional time for recovery.[40]

In the EAP survey, considering people with APDS presenting with gastrointestinal manifestations prior to initiation of leniolisib, remission was demonstrated for 44% of gastrointestinal manifestations. In addition, clinically meaningful improvements were observed in another 40% of gastrointestinal manifestations for people with APDS receiving leniolisib.[64] Upon examining the number of affected individuals with gastrointestinal manifestations prior to initiation of leniolisib, it was found that:[263]

- Remission was demonstrated for gastrointestinal manifestations in 36% of individuals
- Clinically meaningful improvements were observed in 50% of individuals

One individual with colitis at baseline experienced a new colitis event during >2 years of treatment.[263] Further results from the EAP survey are presented in Section B.2.6.8.

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B.2.6.3 Improvements in immune deficiency measures

Reduction in infection rate

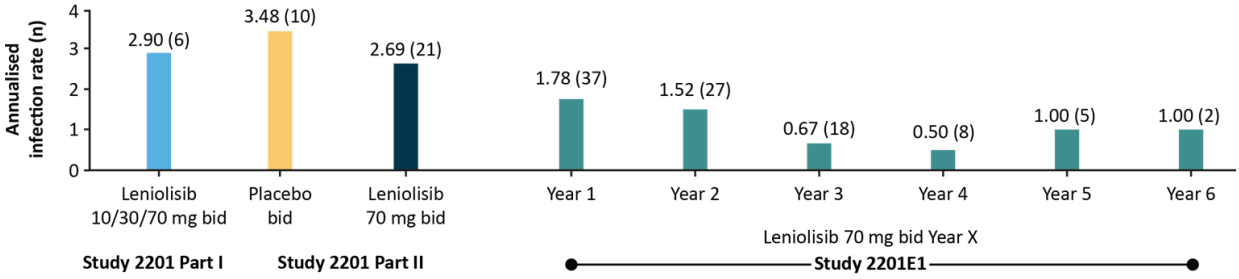
Across all the clinical trials, infections were reported as treatment emergent adverse events (TEAEs) and were grouped as "infections and infestations" by system organ class.[37, 38, 44] Given the significance of severe, recurrent and/or persistent infections as a clinical manifestation of APDS, rates of infections recorded as TEAEs are reported within the efficacy section of this submission. Furthermore, Study 2201E1 included a secondary objective of evaluating the long-term efficacy of leniolisib, by measuring frequencies of infections.[259] As people with APDS are already susceptible to infections, and immunosuppression can increase the risk of infections, both leniolisib clinical trials included additional infection monitoring:

- Investigators specifically enquired about signs and symptoms of infections at each visit;
- Participants were to be reminded of infection risk and to promptly report any symptoms; and
- Participants were to carry their Patient Information Card to show to any other healthcare professional, and request that the investigator was contacted

Reductions in annualised infection rates (safety analysis set)

In Study 2201 Part II, annualised infection rates were lower in participants treated with leniolisib compared to the placebo group (2.690 versus 3.476 infections per year). Accordingly, in Study 2201E1, 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).[38] A **nominally significant decrease in annualised infections rates of 25% was reported with each additional year of leniolisib treatment** (−0.282 infections per year, one-sided p=0.0256; DCO: 13th March 2023).[41] These results demonstrate that long-term treatment with leniolisib leads to a sustained reduction in infections. As complete restoration of immune function is expected to take 2–5 years,[280, 281] further reductions in infection rates are expected over time.

Figure 14. Bar chart of annualised infection rates throughout Study 2201 and Study 2201E1 (safety analysis set)



Footnotes: Annualised rate for Study 2201 Part I and Part II is defined as =((number of infections)/84)*365 per patient. Only on treatment infections were counted up to study Day 84. Other infections that occurred after this day in Part I and Part II were not included in the derivation. Participants should have completed the full time period if they were included in the analysis. For example, a participant with 360 days follow-up in Study 2201E1 should not contribute data to the 'Year 1' bar. A participant with 380 days follow-up in Study 2201E1 should contribute to 'Year 1' but not 'Year 2'. The cut off for the extension study data was 13 March 2023.
Abbreviations: bid: Bis In Die (twice daily); OLE: open label extension.
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Figure 10 based on Table 14.3-2.5.1).[38]

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Supplementary evidence for infection data has been provided in the Appendix including:

- Stability of the levels of markers for EBV and CMV viral infections were recorded in all three clinical trials and are reported in Appendix N.2.3,[17, 27, 37, 38]
- Rates of respiratory infections in Study 2201E1; utilising these data, an externally controlled matched indirect comparison showed significant annualised improvements in respiratory infection rates with leniolisib versus current clinical management (including immunosuppressive therapies and HSCT). Please see Appendix N.2.2 for further information

It is notable that **the reduction in annualised infection rates was observed despite a sustained decrease in use of concomitant IRT, as well as some individuals achieving IRT freedom** during Study 2201E1 (Section B.2.6.3). Additionally, these findings were observed **without an increase in the number of days for which participants were receiving antibiotics** (prophylaxis or acute treatment; Section B.2.6.3). These results indicate that the reduction in rate of infections is associated with leniolisib treatment, rather than concomitant medication usage. Additional supportive real-world evidence regarding annualised infection and hospitalisation rates pre- and post-leniolisib treatment are presented Section B.2.6.8.

Reductions in IRT and antibiotic usage

IRT usage in Study 2201 and Study 2201E1

Participants in Study 2201 and Study 2201E1 were permitted to receive selected concomitant treatments alongside leniolisib and placebo, including IRT (Section B.2.3.3). The number of days of IRT use in Study 2201E1 was analysed post hoc, to assess whether IRT usage changed with long-term leniolisib treatment:

- At baseline of Study 2201 Part II and Study 2201E1, 68% (n=21/31) and 73% (n=27/37) of participants were receiving IRT, respectively.[17, 35]
- At 27 months in Study 2201E1, Kaplan Meier analysis reported that **there was a 30–40% probability of participants being able to reduce IRT usage by at least 50%**.[38, 41]
- During Study 2201E1, 10/27 participants had reduced IRT usage, or achieved and maintained IRT freedom (538–1398 days of IRT freedom at last study visit; DCO: 13th March 2023),[38] further indicating that long-term treatment with leniolisib reduces and halts the need for IRT.
    - Notably, 4/6 participants from Study 2201 Part I had remained IRT-free during the long-term extension study, and two other participants had been maintained on subtherapeutic doses of IgG.[38]
- Figure 15 demonstrates that IRT usage decreased throughout Study 2201 and Study 2201E1 per 3-month period, amongst participants who received IRT; however, this result was not statistically significant (p=0.0817).[38, 41, 42]

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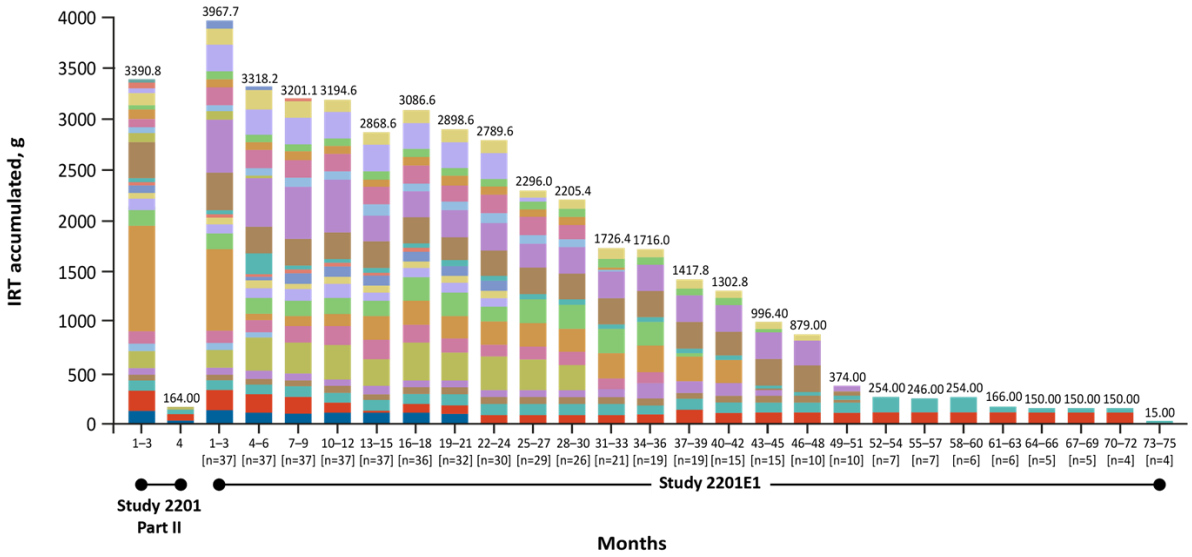
Figure 15. Administered IRT over time during Study 2201 and Study 2201E1 (safety analysis set)



Footnotes: Each colour in the bars represents a participant in Study 2201 and/or Study 2201E1. Part II treatment = leniolisib 70 mg bid and placebo bid. Study 2201E1 treatment = leniolisib 70 mg bid. The cut off for Study 2201E1 was 13th March 2023.
Abbreviations: bid: Bis In Die (twice daily); Ext: extension; IG: immunoglobulin; IRT: immunoglobulin replacement therapy; RCT: randomised controlled trial.
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Figure 14.3-2.2).[38]

By reducing or halting the need for IRT in individuals with APDS, leniolisib is expected to diminish the burden and cost of IRT on patients and the NHS,[52] for example, by reducing the amount of time spent in hospital receiving invasive IRT transfusions,[31] as well as decreasing the associated expense and supporting supply chain easing.[198]

Antibiotic usage in Study 2201 and Study 2201E1

Additionally, despite reduced IRT usage, in Study 2201 Part II and Study 2201E1, the days of **antibiotic usage with leniolisib treatment remained lower than within the placebo arm of Study 2201 Part II**, up to Year 6 (Figure 16).[38, 41, 42] Additionally:

- In Study 2201 Part II, the annualised rate of antibiotic usage in participants treated with leniolisib was 214 medicated days of therapy (DOT) compared to 351 medicated DOT for participants receiving placebo.[38]
- Moreover, in Study 2201 Part II, 42.9% (9/21) of participants receiving leniolisib were reported to use concomitant antibiotics, compared to 80% (8/10) of participants in the placebo arm.[37]

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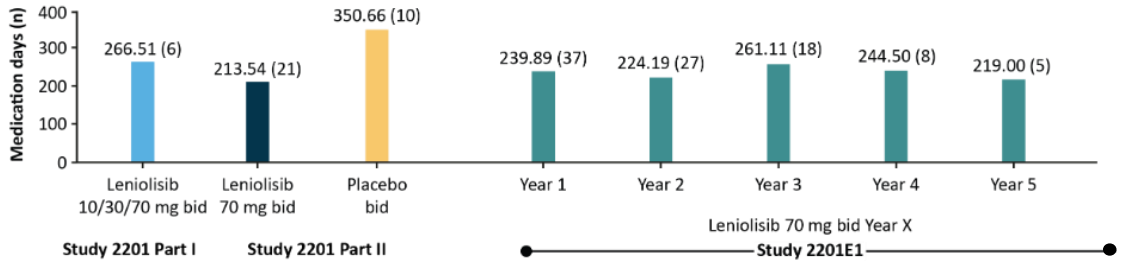
Figure 16. Frequency of antibiotic intake in Study 2201 and Study 2201E1



Footnotes: Medication days (n) is the total annualised number of days of therapy, counted separately for each antibiotic prescribed to individuals with APDS in the trials. The annualised rate of therapy for Study 2201 was defined by the number of days of therapy per patient/84*365. Study 2201 Part I and Part II include treatment up to Day 84. Study 2201E1 includes participants with a full year of treatment (e.g., Year 1=365 days, Year 2=730 days). Antibiotic intake was determined by evaluating concomitant medication recorded for participants during the leniolisib clinical trials; no distinction was made between participants who received antibiotics for acute treatment and/or prophylaxis.[43]
Abbreviations: bid: Bis In Die (twice daily).
Source: Post hoc analyses of Study 2201E1, Pharming Data on File, 2023 (Table 14.1-8.2).[41]

Whilst there was no significant reduction in antibiotic usage over the duration of Study 2201E1 (p=0.18),[38] it is notable that antibiotic intake did not increase with a reduction in IRT (Section B.2.6.3). These findings demonstrate that continued treatment with leniolisib reduces the need for antibiotics and is associated with sustained improvements in immune system functioning. By reducing the need for antibiotics in individuals with APDS, leniolisib presents an opportunity to optimise antibiotic use by reducing the quantity of antibiotics prescribed by the NHS,[43] which is in turn expected to diminish the associated risk of antimicrobial resistance.[56-58]

Hearing loss

During Study 2201 Part I, there was one incidence of deafness reported (not study drug-related); however, there **were no new incidences of deafness reported during Study 2201 Part II** (across both leniolisib and placebo groups) or **Study 2201E1**.[38, 43]

In Exercise 3 of the Expert Consultancy, all five clinicians agreed/somewhat agreed that a reduction in otitis infections would lead to a reduction in incident cases of hearing loss in individuals with APDS.[14] Correspondingly, as described in Section B.2.6.3, leniolisib treatment reduces the rate of infections (including respiratory infections; see Appendix N.2.2).[38, 152] As a result of the reduction in infections (including both otitis and respiratory), leniolisib treatment is expected to reduce the risk of hearing loss.

B.2.6.4 Lung disease (including bronchiectasis-associated airway disease and advanced lung disease)

Lung disease was not investigated as a pre-specified efficacy outcome in the clinical trial programme for leniolisib therefore, lung disease has been addressed in this submission utilising safety data and supplemental post hoc analyses. Given that APDS is a recently described ultra-rare IEI and only safety data and post hoc analyses for lung disease is available from the clinical trials, a supplementary real-world case study is also provided below.

In Study 2201 Part II, an infective exacerbation of bronchiectasis was reported in one participant in the placebo arm and no participants in the leniolisib arm.[37] In the longer-term Study 2201E1, there were **no new cases of infective exacerbations of bronchiectasis reported**.[38]

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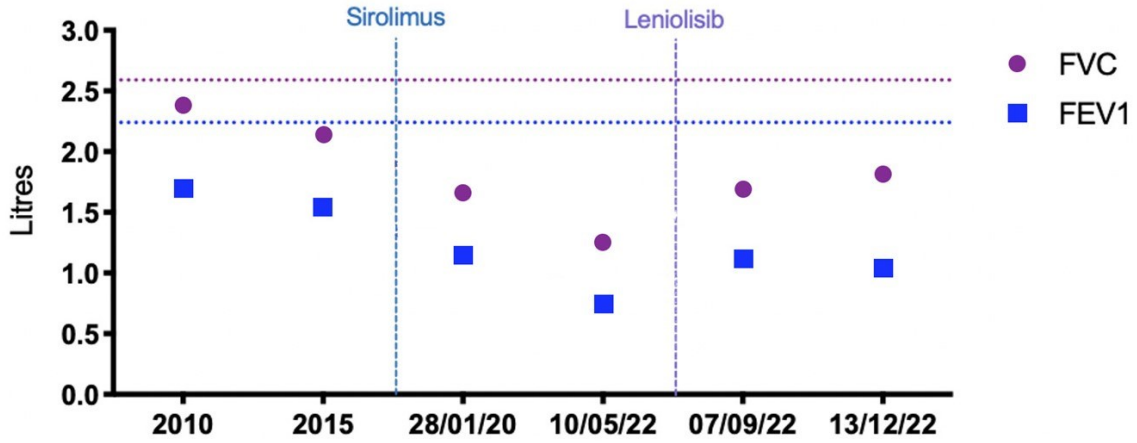
As part of a case study, the long-term effects of leniolisib on bronchiectasis were analysed in six participants who received leniolisib for six years in the clinical trials. Three of the participants did not develop bronchiectasis at any time before or during the OLE; the remaining 3/6 participants had developed bronchiectasis prior to entering Study 2201 Part I. During Study 2201E1, **bronchiectasis did not progress in any these three individuals through six years treatment with leniolisib, additional pulmonary support was not required**, and all were stable at Year 6 of treatment with leniolisib. Moreover, at the latest timepoints with available data for these three individuals, as a proportion of total B cells, mean naïve B cell levels increased from 24.00% at baseline to 82.23%, mean transitional B cell levels decreased from 43.87% to 0.49%, and the CD4:CD8 T-cell ratio normalised from 0.67 to 1.19. As leniolisib normalises immune cells and reduces lymphoproliferation in these individuals, both of which are suspected to be key players in the development of bronchiectasis, it would be reasonable to suspect that leniolisib plays a role in reducing the severity and/or progression of bronchiectasis. These results are likely associated with improvements in HRQoL, with individuals reporting that they have an increased ability to exercise without shortness of breath.[36, 282]

Evidence from an Australian case study of an individual with APDS supplements these data from the leniolisib clinical trials. The individual had a history of recurrent severe respiratory infections and developed bronchiectasis in the second decade of their life. From 2019–2022 (prior to initiation of leniolisib treatment), the individual suffered from 4–6 infections per year and was hospitalised at least 3–4 times per year for infective exacerbations.[283] The individual was assessed for HSCT however, she was deemed too high-risk for a successful HSCT procedure due to her poor lung function. Furthermore, during her latest evaluations in 2022, the individual documented chronic airflow limitation with forced expiratory volume within one second (FEV1) <40% predicted.[283] Since commencing leniolisib treatment in August 2022 (data presented in September 2023), the individual has not had an infective exacerbation nor required hospital admission. Results also highlight **improved oxygen saturation** (SpO_2; 88% to 98% on room air) and **improved lung function after six months of leniolisib treatment** (spirometry FVC: increasing to 1.8 and FEV1: increasing to 1.1).[48, 283]

Figure 17. Lung function improvement over time



Abbreviations: FEV: forced expiratory volume; FVC: forced vital capacity.
Source: Limaye et al., 2023.[48]

In the EAP survey, considering the people with APDS presenting with lung disease prior to initiation of leniolisib, 22% of reported lung disease **manifestations** achieved remission, whilst clinically meaningful improvements were observed in 31% of lung disease manifestations.[64]

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Upon examining the number of affected **individuals** in the leniolisib EAP, it was found that for people experiencing lung disease manifestations prior to the initiation of leniolisib (Table 33):[263]

- Remission was achieved in 29% of individuals
- Clinically meaningful improvements were observed in 24% of people

For individuals without bronchiectasis at baseline (n=17), one individual had a new event of bronchiectasis. Further granular results for progressive lung disease and other serious pulmonary manifestations from the EAP survey are presented in Section B.2.6.8.

In Exercise 3 of the Expert Consultancy, all five clinicians agreed/somewhat agreed that early bronchiectactic changes and other associated airway changes such as inflammatory changes can be reversed if infections are controlled in individuals with bronchiectasis-associated airway disease.[14]

Evidence and expert opinion suggests that **leniolisib treatment prevents the progression of bronchiectasis**, but is also **expected to reduce the risk of long-term organ damage caused by chronic inflammation**,[11, 14, 21, 22] and may have a positive impact on lung function. This in turn diminishes the need for supplementary pulmonary support enabling individuals to return to their lives (e.g. back to university and/or work).[36, 48, 64]

B.2.6.5 Fatigue

Several manifestations of APDS can contribute towards fatigue in people with APDS. Fatigue was not measured as a standalone outcome in the leniolisib clinical trials; however, participant narratives collected during the leniolisib clinical trials and real-world evidence indicate that leniolisib leads to improvement in fatigue/increased energy.

Investigators involved in the leniolisib clinical trials were asked to describe the participants' disease manifestations at the end of study treatment (Study 2201 Part I and Part II) or during the extension study (Study 2201E1), and to provide details on the areas where they observed improvement or worsening during the treatment phase.[37, 38, 44] In Study 2201 Part II, the investigator narratives described positive improvements including increased tolerance for physical activity and decreased fatigue in 70.0% of participants receiving leniolisib versus 44.4% receiving placebo.[17] For example, after treatment with leniolisib participants were able to travel, take fewer naps a day, and socialise with friends and family.[37] In line with the improvements observed in the leniolisib clinical trials, supplemental evidence from the EAP demonstrates that 53.0% of affected individuals had clinically meaningful improvements in chronic fatigue, with 27.0% of affected individuals achieving remission.[64]

Available qualitative patient data reporting leniolisib treatment experience were systematically assessed, including: the participant narratives collected during the clinical trials, case reports, and interviews/narratives from a standalone 2023 qualitative study conducted with APDS patients/caregivers. 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%).[284] Furthermore, this is in line with the observations made by Rao et al., 2024 in a case series of the six participants from Study 2201 Part I with six years follow-up data in Study 2201E1, whereby 5/6 participants experienced an increase in physical capabilities within six months of receiving leniolisib and socialisation within one year of treatment.[282]

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B.2.6.6 Malignancy and mortality

There were no new malignancies reported in Study 2201 Part I and Part II; in Study 2201E1, as of the latest DCO (13th March 2023), a case of classical Hodgkin's lymphoma was reported at Day 750 of the OLE in a participant, which led to treatment discontinuation; this AE was not considered to be related to leniolisib, by the investigator.[38] Three independent clinical assessment reports from clinical experts supported that the onset of Hodgkin's lymphoma was unrelated to leniolisib treatment.[285-287] **No other clinically significant new malignancies were reported in the clinical trial programme, including in participants with a history of lymphoma** (DCO: 13th March 2023).[38] More specifically, there has been no recurrence of lymphoma in the three participants in Study 2201 Part I with a history of lymphoma with five years of exposure to leniolisib.[38] Accordingly, in the supplemental EAP survey, three individuals with APDS had lymphoma prior to starting leniolisib (28/30 physician responses were captured for prior lymphoma) and none have since recurred. However, there was one new event of lymphoma reported in the EAP, which was not associated with leniolisib.[43, 64] In Exercise 3 of the Expert Consultancy, four clinicians agreed/somewhat agreed that a reduction in lymphoproliferation could be associated with a reduced risk of developing lymphoma (see Section B.2.6.2). For further detail, please refer to the Expert Consultancy report.[14]

Given the short study duration and small trial population size, a low number of mortality events were expected during Study 2201 Part II. As such, the effect of leniolisib on mortality was not assessed as an efficacy endpoint in the trial. Safety findings related to discontinuation or death are outlined in Section B.2.10.5.

B.2.6.7 Disease severity and health-related quality of life (HRQoL)

In the absence of validated measures of disease severity in APDS, as well as APDS-specific HRQoL instruments that would be sensitive to the impact of APDS on HRQoL, SF-36 assessment was chosen to provide a broad picture of the impact of APDS and leniolisib treatment on all aspects of HRQoL, including physical functioning and the impact of APDS on everyday life. Furthermore, PtGA assessments offer insights into the disease severity of APDS by providing the patient's perception regarding their own wellbeing due to the impact of APDS. Findings from these measurements were supported by participant narratives collected during the leniolisib clinical trials, as well as evidence from the EAP (see Section B.2.6.8).[17, 27, 35, 38, 64]

SF-36

The SF-36 v2® Health Survey (SF-36v2, hereafter referred to as SF-36) measures HRQoL and has been used in people with IEIs.[288, 289] Baseline results of Study 2201 Part I and Part II, as well as Study 2201E1 are presented in Table 28. In all cases, SF-36 scores for role-physical, general health, social functioning and role-emotional scales were below average for the general population (<47).[37, 44]

Table 28. Baseline SF-36 (norm-based scores) from Study 2201 Part I and Part II, as well as Study 2201E1 (PD analysis set)

SF-36 Scale/Component Summary Measure	Study 2201 Part I	Study 2201 Part II		Study 2201E1
	Leniolisib 10/30/70 mg bid (N=6)	Leniolisib 70 mg bid (N=19)	Placebo bid (N=8)	Total extension (N=31)

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	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Component Summary Measures				
PCS	47.40 (8.92)	44.49 (7.08)	44.06 (8.60)	46.21 (7.21)
MCS	48.02 (8.14)	47.36 (7.98)	45.94 (8.14)	47.67 (8.15)
Scales				
Physical functioning	48.61 (8.36)	47.37 (7.44)	44.86 (12.06)	48.23 (7.36)
Role-physical	46.30 (10.09)	44.39 (9.17)	44.25 (7.18)	45.57 (8.14)
Bodily pain	51.25 (11.49)	49.44 (9.04)	49.90 (9.53)	50.70 (9.19)
General health	42.33 (9.07)	35.84 (7.21)	35.89 (8.47)	38.54 (9.33)
Vitality	50.62 (5.84)	49.16 (9.56)	47.77 (9.39)	50.01 (10.37)
Social functioning	45.64 (10.36)	45.73 (10.17)	44.18 (8.86)	46.83 (9.54)
Role-emotional	44.56 (12.78)	45.36 (8.11)	43.98 (10.85)	45.72 (8.43)
Mental health	51.30 (6.49)	48.25 (9.02)	46.94 (5.93)	48.59 (8.10)

Footnote: Scales are scored from 0–100, with higher scores indicating better health. All scales contribute in varying degrees to a physical component summary (PCS) measure and a mental component summary (MCS) measure.[290] To aid interpretation of the SF-36, norm-based scoring can be utilised, where scores are transformed so that a mean of 50 and a standard deviation of 10 is considered equivalent to the 2009 U.S. general population. As a result, whenever an individual respondent's scale score is below 45, or a group mean scale score is below 47, the implication is that health status is below the average range (shaded in blue).[290, 291]
Source: Study 2201E1 CSR (IA1), Pharming Data on File, 2022 (Table 14.2-4.1)[292] and Study 2201E1 CSR IA2, Pharming Data on File, 2023 (Table 14.2-4.1).[38]

Numerical increases were shown in all SF-36 scales in the leniolisib arm of Study 2201 (Part I and Part II) however, when considering these results, it should be noted that both positive and negative changes in scores were also observed in the placebo arm of Study 2201 Part II, limiting the conclusions that can be drawn from the 12-week data.[37, 44]

In Study 2201E1, **mean scores generally showed an improvement (increase) from baseline for all scales, which were maintained throughout the extension study** as of the DCO: 13th March 2023. The mean scores for the scales of general health and role-emotional increased from baseline, however, mean scores were generally still slightly below the average range for the general population. Mean scores for all other scales met or exceeded the average range. Results for the participants with/without prior exposure to leniolisib were comparable to all extension study participants combined.[38]

In line with the above, during Study 2201 Part I and Part II, no meaningful CfB was observed across any of the SF-36 scales in the leniolisib group.[17, 37, 38, 44] Additionally, analysis of the CfB in Study 2201 Part II at Week 12 did not show a statistically significant difference between the leniolisib and placebo groups, on the PCS (2-sided p=0.8567) or on the MCS (2-sided p=0.7279).[37]

In Study 2201E1, however, **meaningful improvements in HRQoL were demonstrated in the SF-36 PCS at Weeks 12 and 52** (Table 29), with mean scores for CfB exceeding the minimal clinically important difference of 3.4.[38, 41, 293] The norm-based general health scale score improved by 11.04 by Week 156 (three years) as compared with baseline values, in individuals who had values at both timepoints. This improvement can be considered clinically meaningful in people with PIDs.[294]

Table 29. Mean CfB in SF-36 (norm-based scores) over time (Study 2201E1; PD analysis set)

SF-36 Scale/Component	Baseline	Week 12 (n=31)	Week 52 (n=28)	Week 130 (n=19)	Week 156 (n=14)	Week 208 (n=10)	

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Summary Measure	Mean (SD)	Mean CfB (SD)	Mean CfB (SD)	Mean CfB (SD)	Mean CfB (SD)	Mean CfB (SD)	Within-Patient Meaningful Change Threshold for SF-36 v2 Domain Norm-Based Scores[a]
Component Summary Measures							
PCS	46.57 (7.39)	4.84 (5.81)	5.49 (7.28)	3.17 (6.95)	NR	NR	3.4
MCS	47.87 (8.09)	3.00 (8.89)	2.76 (8.86)	0.54 (7.80)	NR	NR	4.6
Scales							
Physical functioning	48.23 (7.36)	3.75 (5.11)	3.61 (5.89)	2.32 (6.20)	-0.14 (10.28)	5.36 (4.95)	4.3
Role-physical	45.57 (8.14)	4.27 (6.41)	4.33 (7.58)	2.84 (8.98)	3.69 (8.24)	2.69 (6.62)	3.4
Bodily pain	50.70 (9.19)	3.14 (8.67)	2.07 (9.01)	3.14 (8.16)	2.65 (5.73)	1.94 (4.82)	6.2
General health	38.54 (9.33)	8.12 (9.31)	7.23 (10.12)	10.36 (10.03)	11.04 (8.65)	9.79 (5.46)	7.2
Vitality	50.01 (10.37)	4.03 (10.10)	4.99 (10.67)	3.91 (12.25)	3.18 (8.03)	10.1 (7.16)	6.2
Social functioning	46.83 (9.54)	3.07 (8.65)	3.58 (8.39)	1.58 (12.06)	0.36 (7.21)	-5.01 (7.92)	6.9
Role-emotional	45.72 (8.43)	3.15 (7.86)	3.11 (7.24)	0.73 (10.16)	-1.49 (9.13)	0.70 (5.16)	4.5
Mental health	48.59 (8.10)	3.46 (9.02)	2.15 (8.78)	3.86 (9.65)	4.11 (5.96)	5.76 (6.24)	6.2

Footnotes: Yellow highlighting indicates where results for mean CfB exceeded the within-participant meaningful change thresholds for the SF-36 v2 domain norm-based scores. [a]Based on Table 10.2, page 176 of the User Manual for SF-36v2 Health survey, 3rd Edition (2011).[290]
Abbreviations: CfB: change from baseline; PCS: physical component summary; PD: pharmacodynamics; NR: not reported; SF-36: Short Form-36; SD: standard deviation.
Source: Pharming Data on File, 2024,[263] Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 14.2–4.1),[38] and SF-36 Evidence Dossier, Pharming Data on File, 2022.[294]

Based on the SF-36 results from Study 2201E1, a post hoc responder analysis was performed, to assess the proportions of participants experiencing a ≥3.4 CfB at Week 12 in the SF-36 PCS, or a ≥7.2 CfB at Week 12 in the general health scale (corresponding to the meaningful change thresholds).[41] Results from this post-hoc analysis (Appendix N.2.4) demonstrated that substantial proportions of participants experienced meaningful changes in general health and PCS scores throughout Study 2201 Part I and II, and Study 2201E1.[41, 42]

In addition to the clinical trial data, a case study of an adolescent participant enrolled in Study 2201E1 reported an initial inability to partake in sports or attend school due to fevers and overall weakness prior to treatment; after one year of treatment with leniolisib resulting in normalisation of key lymphocyte subsets, the participant began boxing, attending school, and medications reduced from four to one.[295]

Together, these findings demonstrate that APDS has a wide-reaching impact on the HRQoL of affected individuals, with role-physical, general health, social functioning and role-emotional

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scales consistently below average for the general population at baseline of Study 2201 Part I, Part II and Study 2201E1. With leniolisib treatment, numerical increases from baseline were shown in all SF-36 scales in Study 2201 Part I and Part II, which were maintained throughout Study 2201E1 for leniolisib treatment groups, with CfB and responder analyses demonstrating **meaningful long-term changes in general health and PCS scores**.

PtGA

In the leniolisib clinical trials, PtGA, a PRO was measured using a visual analogue scale (VAS) ranging from 'very poor' (0) to 'very good' (100). Participants were asked: 'Considering all the ways APDS affects you, please indicate with a vertical mark (I) through the horizontal line how well you are doing'.[37, 38, 44] Based on estimates from the literature, and data from Study 2201 Part I and II, a change of approximately 10–20 points on the PtGA scale can be used as a within-participant meaningful change threshold.[296] As APDS is a progressive disease,[12, 13] a decrease in PtGA scores would be expected over time without treatment.

- Meaningful improvements in PtGA scores were found during Study 2201 Part I, with participants' wellbeing related to APDS showing a mean increase of 10.5 mm from baseline to Week 12 (SD: 10.7 mm).[27, 44]
- These improvements in PtGA scores were replicated in Study 2201 Part II. While the mean CfB in PtGA scores in the leniolisib group was 13.05 mm (indicating a meaningful change; SD: 20.71 mm) at Week 12, the mean CfB in the placebo group was −2.25 mm (SD: 28.95 mm; Table 30). The analysis of CfB at Week 12 showed no statistically significant difference between the leniolisib and placebo groups (2-sided p=0.2113).[271, 296]

Table 30. Mean CfB to Week 12 in PtGA of APDS (VAS scale) [Study 2201 Part II; PD analysis set]

Treatment arm	Mean CfB (SD)	Comparison of leniolisib to placebo		
		Adjusted mean difference	95% CI	2-sided p-value
Leniolisib 70 mg bid (n=19)	13.05 (20.71)	9.25	−5.65, 24.14	0.2113
Placebo (n=8)	−2.25 (28.95)			

Abbreviations: APDS: activated PI3K delta syndrome; bid: Bis In Die (twice daily); CfB: change from baseline; CI: confidence interval; PD: pharmacodynamics; PtGA: Patient Global Assessment; SD: standard deviation; SE: standard error of the mean; VAS: visual analogue scale.
Source: Study 2201 Part II CSR Version 2.0, Pharming 2022 (Section 11.2.2).[37]

During Study 2201E1, participants were asked the same question as in Study 2201 for PtGA. However, the scores were transformed (flipped) with a lower score consequently indicating a higher wellbeing, instead of lower wellbeing. The **PtGA scores in Study 2201E1 remained improved versus baseline, indicating a long-term, stabilised increase in wellbeing (and reduction in disease severity) for participants treated with leniolisib** (Table 31); the mean CfB generally remained greater than the meaningful change threshold of >10 mm throughout the Study 2201E1.[35, 38, 296]

Table 31. Mean CfB to Weeks 12, 182 and 208 in PtGA of APDS (VAS scale) [Study 2201E1; PD analysis set]

	Week 12	Week 182	Week 208

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Treatment	n	Mean CfB (SD)	n	Mean CfB (SD)	n	Mean CfB (SD)
Leniolisib	37	-14.66 (21.42)	15	-19.49 (28.44)	10	–25.63 (26.62)

Footnotes: The PtGA scores have been transformed (flipped) so that a lower score indicates a higher wellbeing.
Abbreviations: APDS: activated PI3K delta syndrome; CfB: change from baseline; PD: pharmacodynamics; PtGA: Patient Global Assessment; SD: standard deviation; VAS: visual analogue scale.
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 14.2-6.1).[38, 41]

Supplemental evidence

Furthermore, supplemental evidence highlights that:

- Thematic analysis of available qualitative evidence (including participant narratives collected during the clinical trials, case reports, and interviews/narratives from a standalone 2023 qualitative study conducted with APDS patients/caregivers), found that leniolisib had a positive impact on APDS manifestations and patient HRQoL, with 31/36 (86.1%) participants experiencing improvement in ≥1 manifestation or HRQoL impact.[284]
- In the EAP, leniolisib treatment was associated with clinically meaningful improvements in a wide range of disease manifestations, with some individuals achieving remission (see below), indicating a reduction in disease activity.[64]

B.2.6.8 Real-world evidence from the EAP and literature

The clinical SLR and subsequent targeted searches, conducted to search for evidence on the efficacy and safety of leniolisib for the treatment of people with APDS (interventional or observational studies), identified eight studies reporting real-world data (see Section B.2.1 and Appendix D). Of these seven studies, five provided evidence that can be attributed to leniolisib (as opposed to concomitant treatment). The results of these five studies corroborate the findings in the clinical trial programme for leniolisib, demonstrating benefits of the treatment in normalising immunophenotypes, and in reducing the severity of APDS manifestations. Supplementary real-world evidence sourced from published literature and case studies has been summarised in Table 34.

In addition, Pharming have established a global EAP for individuals with APDS who were unable to enrol within the clinical trial programme to receive leniolisib treatment; a total of 72 individuals in the EAP have received leniolisib, including six individuals with APDS across three centres in the UK.[43] A team from Great Ormond Street Hospital, London are undertaking a study comprising of approximately 20 individuals with APDS that have received leniolisib in the EAP across Europe, including the UK. Their findings are due to be presented at the Inborn Errors Working Party conference, September 2024. Finally, as described in Section B.2.3.4, a total of 21 physicians treating 30 individuals in the EAP responded to an anonymised survey:

- In the EAP, reported mean annual infection and hospitalisation rates were >50% lower during leniolisib treatment than pre-treatment (see Figure 18), supplementing the reduced rate of infections, as well as antibiotic and IRT usage presented in Section B.2.6.3.[64]
    - Moreover, intra-patient assessment of infections and hospitalisation rates using historical National Institutes of Health data also showed that **leniolisib treatment led to reductions in annualised infection** (mean difference, pre- vs post-leniolisib treatment initiation: 2.723, [95% CI: 1.001–4.437], p=0.0004) **and hospitalisation rates** (mean

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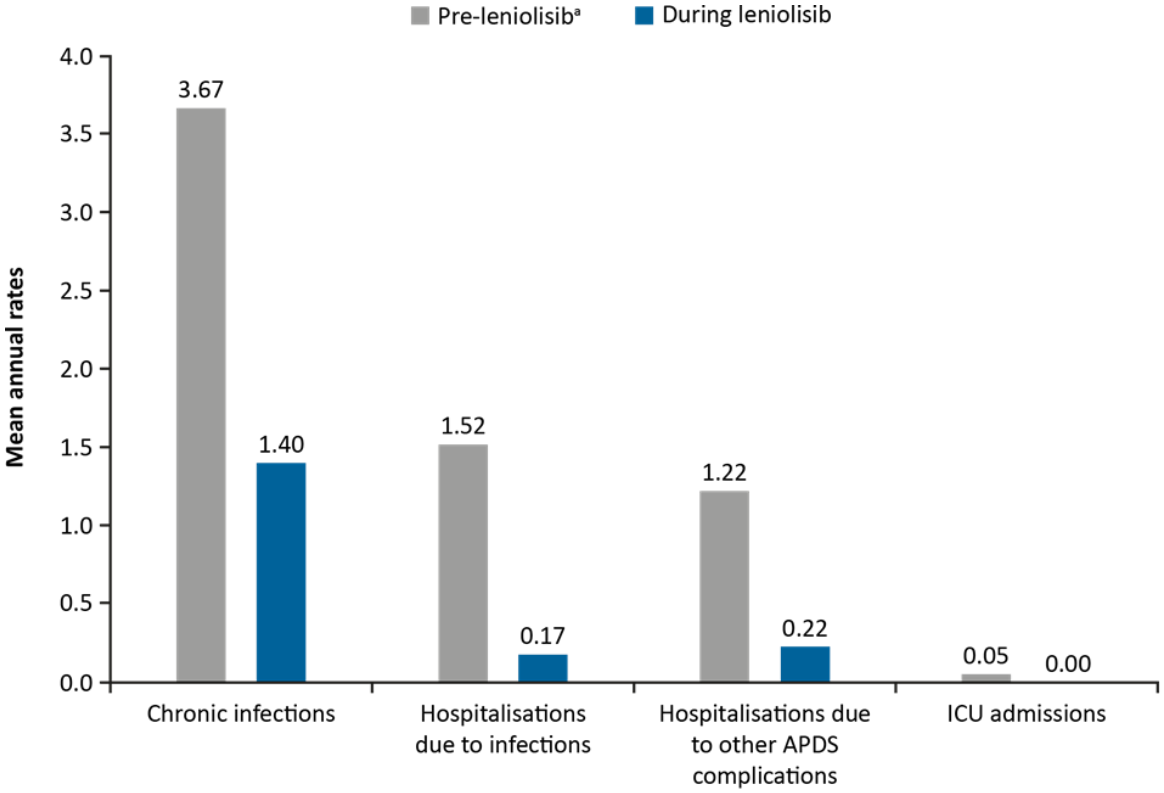
difference, pre- vs post-leniolisib treatment initiation: 0.297, [95% CI: -0.093–0.687], p=0.054).[252]

Figure 18. Annual rates of infections and hospitalisations recorded in the EAP physician survey (N=21 physicians treating 30 individuals in the EAP)



Footnote: [a]Infection rates were captured through physician feedback and annual rates were approximated within the previous three years pre-treatment, by physicians. Length of time on leniolisib varied, and as such mean annual rates were used to minimise bias.
Abbreviations: APDS: activated PI3Kδ syndrome; ICU: intensive care unit.
Source: EAP Physician Survey, Pharming Data on File, 2024.[64]

- For non-infectious manifestations, leniolisib was associated with clinically meaningful improvements or remission in 63% (pulmonary) to 93% (organomegaly) of affected domains (Table 32), with 27% and 21% of pulmonary or organomegaly domains going into remission, respectively[64]
- Additionally, 92% and 96% of affected individuals had clinically meaningful improvements or remission in chronic fatigue and lymphoproliferation, respectively.[64] These data supplement the results presented in Section B.2.6.2 and Section B.2.6.4 regarding the manifestations associated with immune dysregulation and lung disease experienced by individuals with APDS, respectively
- One individual developed lymphoma (assessed as unrelated to leniolisib); among three individuals who had a history of lymphoma, none recurred (Table 33)[64]

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Table 32. Non-infectious APDS manifestations recorded in the EAP physician survey

Non-infectious complication	Pre-leniolisib, n (N=30)	Post-leniolisib reports available, n	Change versus pre-leniolisib			
			Remission, n (%)	Meaningful improvement, n (%)	% domains with at least meaningful improvement, n (%)	% domains worsening or new[b], n (%)
Reported as total responses for multiple affected domains (therefore n can be >30)						
Lymphadenopathy	57	51	22 (39)	23 (40)	45 (79)	0 (0)
Lymphonodular hyperplasia	14	11	4 (29)	6 (43)	10 (71)	0 (0)
Gastrointestinal manifestations	25	23	11 (44)	10 (40)	21 (84)	1 (4)
Pulmonary	36	30	8 (22)	11 (31)	19 (53)	1 (3)
Bronchiectasis	14	11	1 (7)	3 (21)	4 (29)	1 (7)
Progressive lung disease	4	3	0 (0)	3 (75)	3 (75)	0 (0)
Organomegaly	30	28	6 (20)	20 (67)	26 (87)	0 (0)
Cytopenia	23	21	8 (35)	8 (35)	16 (70)	1 (4)
Reported as number of affected individuals						
Lymphoproliferation	25	24	5 (20)	18 (72)	23 (92)	0 (0)
Lymphoma	0[a]	1	NA	NA	NA	1 (100)
Chronic fatigue	15	13	4 (27)	8 (53)	12 (80)	0 (0)

Footnote: [a]Three individuals had a history of lymphoma, all of whom were in remission upon starting leniolisib treatment. [b]The four events observed in the 'worsening or new' category were all new events, which were consistent with the underlying disease.
Abbreviations: APDS: activated PI3Kδ syndrome; NA: not applicable.
Source: EAP Physician Survey, Pharming Data on File, 2024.[64]

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Table 33. Non-infectious APDS manifestations recorded in the EAP physician survey (presented as the number of affected individuals)

Non-infectious complications	Non-infectious complications present at start of leniolisib initiation								No non-infectious complications at start of leniolisib initiation		
	N	Months follow-up	Remission, n (%)	Meaningful improvement, n (%)	No change, n (%)	Worse, n (%)	New symptom, n (%)	Missing[a], N (%)	N	Months follow-up (mean)	Symptoms developed, n (%)
Lymphoproliferation	**25**	**14.0**	**5 (21)**	**18 (75)**	**1 (4)**	**0 (0)**	**NR**	**1**	**5**	**11.4**	**0 (0)**
Cytopenia	**11**	**13.9**	**4 (40)[b]**	**4 (40)[b]**	**2 (20)**	**0 (0)**	**0 (0)**	**1**	**19**	**13.4**	**1 (5)**
Thrombocytopenia	7	11.0	3 (43)	2 (29)	2 (29)	0 (0)	0 (0)	0	23	13.8	0 (0)
Anaemia	8	10.9	3 (43)	3 (43)	1 (14)	0 (0)	0 (0)	1	22	14.6	1 (5)
Leukopenia	6	12.0	1 (20)	3 (60)	1 (20)	0 (0)	0 (0)	1	24	14.0	0 (0)
Other	1	24.0	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0	29	13.2	0 (0)
All reports[c]	21	--	8 (38)	8 (38)	4 (19)	0 (0)	1 (5)	--	--	--	--
Gastrointestinal	**16**	**15.6**	**5 (36)**	**7 (50)[d]**	**1 (7)[e]**	**0 (0)**	**1 (7)**	**2**	**14**	**11.4**	**0 (0)**
Colitis	8	15.0	1 (13)	6 (75)	0 (0)	0 (0)	1 (13)	0	22	13.1	0 (0)
Obstruction	1	24.0	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0	29	13.2	0 (0)
Colonic polyposi	2	13.5	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	0	28	13.6	0 (0)
Chronic diarrhoea	4	17.3	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0	26	13.0	0 (0)
Haematochezia	2	13.5	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0	28	13.6	0 (0)
Low weight/weight loss	7	15.9	2 (40)	2 (40)	1 (20)	0 (0)	0 (0)	2	23	12.9	0 (0)
Serious other	1	9.0	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0	29	13.8	0 (0)
All reports	23	--	11 (48)	10 (43)	1 (4)	0 (0)	1 (4)[f]	--	--	--	--
Pulmonary	**21**	**13.6**	**5 (29)**	**4 (24)[g]**	**8 (47)[h]**	**0 (0)**	**0 (0)**	**4**	**9**	**13.7**	**1 (11)**
Bronchiectasis	13	13.9	1 (8)	3 (23)	6 (46)	0 (0)	0 (0)	3	17	13.3	1 (6)
Obstruction	4	16.5	0 (0)	3 (75)	1 (25)	0 (0)	0 (0)	0	26	13.2	0 (0)
Shortness of breath	5	11.4	2 (50)	1 (25)	1 (25)	0 (0)	0 (0)	1	25	14.0	0 (0)
Asthma	3	17.0	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	1	27	13.2	0 (0)

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Progressive lung disease	4	6.0	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	1	26	14.8	0 (0)
Serious other	6	15.5	5 (83)	1 (17)	0 (0)	0 (0)	0 (0)	0	24	13.1	0 (0)
All reports	30	--	8 (27)	11 (37)	10 (33)	0 (0)	1 (3)	--	--	--	--

Footnote: [a]Missing responses not counted in the denominator for percentage calculations. [b]One individual had remission of thrombocytopenia, with meaningful improvement in anemia and leukopenia. In the cytopenia row this individual is counted once as a "meaningful improvement". [c]"All reports" presents the total number of symptom reports as N and each number of symptom change reports. Individuals may have multiple symptoms responding, and all are reported in this row. [d]One individual had remission of haematochezia and low weight, with meaningful improvement in colitis and colonic polyposis. In the Gastrointestinal row this individual is counted once as "meaningful improvement". [e]One individual had meaningful improvement in colitis but no change in low weight. In the Gastrointestinal row this individual is counted once as "meaningful improvement". [f]One individual with colitis at baseline experienced a new colitis event during >2 years of treatment of leniolisib, as well as complete remission of baseline GI obstruction symptoms and low body weight. [g]One individual had remission of shortness of breath, with meaningful improvement in bronchiectasis. In the Pulmonary row this individual is counted once as "meaningful improvement". [h]One individual had meaningful improvement in obstructive symptoms but no change in bronchiectasis. Another individual had remission of shortness of breath but no change in asthma. Another individual had remission of "serious other", meaningful improvement in progressive lung disease and obstruction, but no change in bronchiectasis. In the Pulmonary row these three individuals are only counted as "no change".
Abbreviations: NR: not reported.
Source: Pharming Data on File, 2024.[263]

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Table 34. Real-world of compassionate use of leniolisib in individuals with APDS sourced in published literature and case studies

Real-world evidence	Geography (N; age range)	Outcomes
Bloomfield *et al* (2021)	Czech Republic (8; 6–30 years old)	• 3/8 individuals (38%) had elevated IgD levels, which were normalised in individuals on leniolisib. Although the function of IgD is poorly understood, IgD is present on naïve B cells and may be involved in regulating B cell development and antibody-mediated immune responses.[297] • Leniolisib benefitted all patients who received treatment (4/8; 50%), particularly in reducing lymphoproliferation.
Conrey *et al* (2021)	United States (NR; NR)	• By comparison of immune profiles of individuals with APDS at baseline to healthy controls, changes in T cell activation markers, inhibitory receptors and transcription factors were associated with alterations in T cell activity (activation and exhaustion). The alterations in the activity of T cells of individuals with APDS identified in this study were found to be partially corrected by targeted leniolisib treatment.
Rivalta *et al* (2021)	Italy (4; 6–34 years old)	• Two patients were treated with leniolisib with good tolerance and improvement in symptoms and quality of life. • Leniolisib use with continued cotrimoxazole prophylaxis three days per week. However, this study found that this treatment regimen reduced the individual's need for IRT to 4 g every 10 days (230 mg/kg/4 weeks). • In this individual with APDS, authors also identified intolerance to leniolisib of more than 30 mg daily due to occurrence of painful ulcers in the mouth and lips. This side effect was controlled with 1 mg daily of colchicine (an anti-gout agent).
Semeraro *et al* (2021)	France (3; 4–27 years old)	• Prior to treatment with leniolisib, all patients experienced severe APDS manifestations despite IRT and long-term immunosuppressive treatment. • One individual (P3) received leniolisib 70 mg bid, whereas the other two individuals (P1 and P2) weighed <45 kg and received lower doses (leniolisib 30 mg or 40 mg bid, respectively). • All individuals presented significant clinical improvements, including significant reduction in lymphoproliferation, splenomegaly and gastrointestinal manifestations, no other severe bacterial or viral infections and global improvements in quality of life, with one individual recovering to normal job activity and family life.
Klemann *et al* (2023)	Germany (1; 20 years old)	• As a result of continuing disease progression (despite treatment with IRT, antibiotics and mTOR inhibitors), an individual with APDS underwent HSCT (10/10 matched sibling donor) with intensive conditioning.

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		• Post-HSCT, the individual experienced autologous reconstitution alongside severe symptoms such as diarrhoea and recurrent sepsis and was offered leniolisib treatment. Leniolisib treatment (initiated July 2021) resulted in a significant reduction in the burden of infection leading to discontinuation of antibiotic prophylaxis (January 2023) and a significant improvement in quality of life (observation in early 2023). • This evidence suggests that leniolisib treatment may be offered to individuals with APDS where HSCT was unsuccessful.
Doroudchi *et al* (2024)[a]	United States (3; 7–24 years old)	• Three patients with APDS with refractory IgA vasculitis were treated with leniolisib. Vasculitis in all three patients resolved after treatment with leniolisib. • Case 1: 19-year-old male experienced recurrent infections and severe IgA vasculitis and achieved complete remission of vasculitis after 21 months on leniolisib therapy. • Case 2 and 3: 24-year-old female and 7-year-old female both had recurring IgA vasculitis managed with leniolisib, leading to response within 2 months for both individuals, and sustained remission for 16 and 10 months, respectively. • Across the three patients, the severity of IgA vasculitis varied and despite different treatment strategies, there was no improvement in their cutaneous disease until treatment with leniolisib.

Footnote: [a]Doroudchi *et al* (2024) was excluded from the clinical SLR during the full text review as it did not report on outcomes within the inclusion criteria for the SLR, based on those specified in the NICE final scope.
Abbreviations: APDS: activated PI3Kδ syndrome; HSCT: haematopoietic stem cell transplant; IgD: immunoglobulin D; IRT: immunoglobulin replacement therapy; mTOR: mammalian target of rapamycin.
Source: Bloomfield et al., 2021,[106] Conrey et al., 2021,[298] Doroudchi et al., 2024,[299] Klemann et al., 2023,[260] Rivalta et al., 2021[300] and Semeraro et al., 2021.[301]

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B.2.7 Subgroup analysis

Summary of subgroup analyses

Results of the co-primary endpoints of Study 2201 Part II in the overall populations were generally consistent across subgroups defined by genetic diagnosis (APDS1 versus APDS2), age group (<18 years versus ≥18 years) and sex (female versus male). Results for individual subgroups must however be treated with caution, due to low sample sizes for many of the subgroups.[42]

Study 2201 and Study 2201E1 investigated the impact of leniolisib across the anticipated licensed population.[17, 27, 35] For Study 2201 Part II, pre-specified subgroup analyses by age (<18 years and ≥18 years) were conducted. Subgroup analysis by sex (male and female) was added to the SAP prior to database lock, and subgroup analysis by genetic diagnosis (APDS1 and APDS2) was added post database lock.[255, 271]

Although the population of Study 2201 Part I included both adolescent and adult participants, subgroup analysis by age (<18 years and ≥18 years) was not performed,[44] due to limited sample size. In addition, in Study 2201E1, all participants were included in all analysis sets. Analyses split by prior treatment (previous leniolisib and previous placebo) were also provided in case prior treatment affected the results of the study; these results can be found in the tables, listings and figures for Study 2201E1.[38] No subgroup analyses based on demographic or clinical characteristics were performed for Study 2201E1.[38]

Subgroup results for the co-primary endpoints of Study 2201 Part II are presented in Appendix E. Across both co-primary endpoints (proportion of naïve B cells out of total B cells and log_{10}-transformed SPD of index lesions), the 95% CIs for the difference in adjusted mean change overlapped for most subgroups, including genetic diagnosis, age and prior mTOR treatment. As an exception, the 95% CIs for the CfB in the log10 transformed SPD between sexes did not overlap, though this may be an artefact due to the small sample sizes. The 95% CI for female individuals with APDS for this parameter just crosses zero but numerical benefit is seen. Similarly, the 95% CI for individuals with APDS aged <18 years old crosses zero for both co-primary endpoints;[42] no meaningful conclusions can be drawn as this is likely due to the smaller sample size of the subgroup.

In summary, results were generally consistent between the overall population and the subgroups.[42] Results for individual subgroups must however be treated with caution, due to low sample sizes for many subgroups.

B.2.8 Meta-analysis

As Study 2201 Part II represents the only RCT evaluating the efficacy and safety of leniolisib versus placebo for the treatment of APDS in adults and adolescents 12 years of age and older,[17] no meta-analysis was performed.

B.2.9 Indirect and mixed treatment comparisons

Study 2201 Part II evaluated the efficacy and safety of leniolisib versus placebo with selected concomitant treatments permitted, in line with the NICE final scope. Whilst restrictions on some treatments were applied in the leniolisib clinical trials to ensure robustness of results, externally

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controlled indirect matched comparisons of changes in IgM levels and respiratory infection rates between leniolisib and current clinical management in the UK provide results consistent with those from Study 2201 Part II (see Appendix N.2.2).

B.2.10 Adverse reactions

Summary of safety results for leniolisib

- Leniolisib was generally well tolerated by all participants in Study 2201 Part I and Part II, with an overall AE profile comparable to placebo; leniolisib remained generally well tolerated with long-term therapy during Study 2201E1.[17, 27, 35, 38]
- Across the three leniolisib clinical trials, 82.0% (433/528) and 10.0% (53/528) AE/TEAEs reported by participants who were administered leniolisib were Grades 1–2 or Grades 3–4, respectively.[38] In Study 2201 Part II, when compared to placebo, the leniolisib group reported fewer study-drug related AEs (23.8%, [5/21] for leniolisib versus 30.0%, [3/10]) for placebo group).[17] In Study 2201 and Study 2201E1, none of the AEs/TEAEs reported that led to discontinuation or the two deaths were determined to be study drug related by investigators.[17, 35, 38]

The safety profile of leniolisib compared to placebo is informed by 12 weeks of data from Study 2201 Part II. Supplementary safety evidence is provided from the long-term ongoing Study 2201E1 and Study 2201 Part I, as well as an ongoing EAP and commercial availability in the US.[17, 27, 35, 38, 43, 64]

Leniolisib was generally well tolerated by all participants in Study 2201 Part I and Part II, with an overall AE profile comparable to placebo; leniolisib remained generally well tolerated with long-term therapy of up to six years during Study 2201E1 (DCO: 13th March 2023).[17, 27, 35, 38] Most of the AEs and SAEs that were reported across the trials were consistent with known events in APDS and there were no important identified risks associated specifically with leniolisib.[37, 38] Across the clinical trials and EAP, with over 200 years of exposure to leniolisib treatment, only seven individuals with APDS have discontinued leniolisib treatment.[263]

B.2.10.1 Exposure

The extent of exposure to leniolisib within each of the leniolisib clinical trials is shown in Table 35. In Study 2201E1, 30/37 participants (81.1%) had ≥96 weeks (approximately two years) of leniolisib exposure, and 5/37 participants (13.5%) had ≥5 years (≥260 weeks) of leniolisib exposure.[38] Overall, there are available data on participants receiving leniolisib for up to six years, with a median exposure of three years.[36, 38]

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Table 35. Leniolisib exposure across Study 2201 Part I and Part II and Study 2201E1

Study	Study 2201 Part I	Study 2201 Part II	Study 2201E1
Number of participants enrolled	6	31 Leniolisib arm: 21 Placebo arm: 10	37
Leniolisib dosing	10, 30, and 70 mg bid for four weeks sequentially	70 mg bid for 12 weeks	70 mg bid for up to six years
Median duration of leniolisib exposure (range), weeks	11.93 (11.9–12.1)	12.14 (11.7–12.4)	154.71 (62.3–312.9)

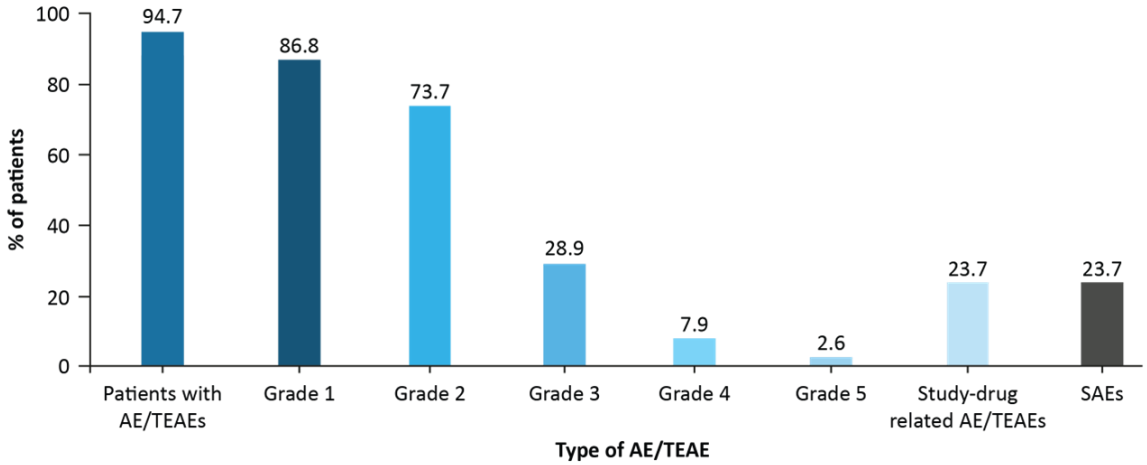
Abbreviations: bid: Bis In Die (twice daily).
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 9).[38]

B.2.10.2 Overview of AEs/TEAEs

Figure 19 presents a summary of the AE/TEAEs reported in participants in Study 2201 Part I and II, and Study 2201E1, with up to six years of exposure to leniolisib. An overview of overall incidence of AE/TEAEs is presented in Table 36.[17, 27, 35, 38] In Study 2201 Part II, when compared to placebo, the leniolisib group reported fewer study-drug related AEs (23.8%, [5/21 participants] for leniolisib versus 30.0%, [3/10 participants]) for placebo group) [Table 36].[17] Across the three trials, 82.0% (433/528) AE/TEAEs reported by participants who were administered leniolisib were Grade 1 or Grade 2.[38]

There were no discontinuations in Study 2201 (Part I and II). Six participants discontinued study treatment in Study 2201E1, of which two were related to an AE but not to study treatment. Across the three leniolisib clinical trials, there are two deaths, both of which were not related to the study treatment.[37, 38, 44] Please refer to Section B.2.10.5 for further detail.

Figure 19. Percentage of participants receiving leniolisib (N=38) reporting AE/TEAEs across Study 2201 (Part I and Part II) and Study 2201E1



Footnotes: Grades 1 to 4 record AE/TEAEs that were mild, moderate, severe or life-threatening, respectively. Grade 5 AEs/TEAEs signify death.
Abbreviations: AE: adverse event; no.: number; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: Study 2201E1 CSR IA2, Pharming Data on File, 2023 (Table 12).[38]

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Table 36. Overall incidence for AEs/TEAEs across Study 2201 (Part I and Part II) and Study 2201E1 (safety analysis set)

	Study 2201 Part I			Study 2201 Part II		Study 2201E1 (leniolisib 70 mg bid)			Total Leniolisib N=38 nE, nS (%)
	Leniolisib 10 mg bid N=6 nE, nS (%)	Leniolisib 30 mg bid N=6 nE, nS (%)	Leniolisib 70 mg bid N=6 nE, nS (%)	Leniolisib 70 mg bid n=21 nE, nS (%)	Placebo bid n=10 nE, nS (%)	Previous Leniolisib n=26 nE, nS (%)	Previous placebo n=9 nE, nS (%)	Total Extension N=37 nE, nS (%)	
AEs/TEAEs, Participants with AEs/TEAEs	4, 2 (33.3)	3, 2 (33.3)	11, 4 (66.7)	92, 18 (85.7)	46, 9 (90.0)	286, 24 (92.3)	112, 8 (88.9)	418, 34 (91.9)	528, 36 (94.7)
Rates per participant-year[a]: AEs/TEAEs	8.9	6.5	22.1	18.0	17.9	3.3	4.9	3.6	4.2
Study drug-related AEs/TEAEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	6, 5 (23.8)	8, 3 (30.0)	4, 3 (11.5)	2, 1 (11.1)	7, 5 (13.5)	13, 9 (23.7)
Serious AEs/TEAEs[b]	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	5, 3 (14.3)	6, 2 (20.0)	11, 5 (19.2)	25, 3 (33.3)	36, 8 (21.6)	41, 9 (23.7)
Deaths[c]	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (10.0)	1, 1 (3.8)	0, 0 (0.0)	1, 1 (2.7)	1, 1 (2.6)

Footnotes: AEs or TEAEs have been classified according to the respective clinical study reports. [a]AE rate participant year = Total_AEs / Total_pt_follow-up_yrs (AE rate in units of events per participant-year). [b]SAEs were defined as AEs which met any of the following criteria: fatal or life-threatening; resulted in persistent or significant disability/incapacity; constituted a congenital anomaly/birth defect; required inpatient hospitalisation or prolongation of existing hospitalisation (unless hospitalisation was for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, elective or pre-planned treatment for a pre-existing condition that was unrelated to the indication under study and had not worsened since the start of study drug, treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission, social reasons and respite care in the absence of any deterioration in the participant's general condition) or medically significant, defined as an event that jeopardised the participant or required medical or surgical intervention. [c]Rao et al., 2023 reports no deaths in Study 2201 Part II as the publication only reported AEs that occurred within 30 days after the study had ended. For further information on the death recorded for the participant receiving placebo in Study 2201 Part II, please refer to Section B.2.10.5.
Abbreviations: AE: adverse event; bid: Bis In Die (twice daily); N: number of participants studied; nE: number of AE events in the category; nS: number of participants with at least one AE in the category; TEAE: treatment-emergent adverse event.
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 12).[38]

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B.2.10.3 Common AEs/TEAEs

Incidence of common AEs/TEAEs

In Study 2201 Part II, the incidence of AEs was similar between individuals treated with leniolisib (85.7%, [18/21 participants]) and those treated with placebo (90.0%, [9/10 participants]).[17] The majority of AEs by system organ class in Study 2201 Part II were generally comparable between the treatment groups (Appendix F), the most common being infections and infestations (52.4%, [11/21] for the leniolisib group versus 40.0%, [4/10] for the placebo group), followed by gastrointestinal disorders (33.3% [7/21] for the leniolisib group versus 40.0%, [4/10] for the placebo group) and skin and subcutaneous tissue disorders (33.3% [7/21] for the leniolisib group versus 10.0%, [1/10] for the placebo group).[37]

The primary outcome for the OLE, Study 2201E1, was to assess the long-term safety and tolerability of leniolisib. Prior to the DCO (13th March 2023), over the median duration of three years of exposure to leniolisib in Study 2201E1, 91.9% (34/37) of participants reported a total of 418 TEAEs.[38] In all 37 participants, the highest incidence of TEAEs by organ class were infections and infestations (83.8%, [31/37]), gastrointestinal disorders (62.2%, [23/37]) and investigations (48.6%, [18/37]).[38] As 11 participants enrolled into Study 2201E1 with no prior exposure to leniolisib (including two participants who previously received another PI3Kδ inhibitor), AEs were separated and investigated to ensure a similar AE profile existed between those with previous exposure to leniolisib (n=26) or previous exposure to placebo (n=9). Although participants with previous exposure to leniolisib reported a higher number of TEAEs (92.3%, [24/26]) than participants with previous exposure to placebo (88.9%, [8/9]), the AE rate per participant-year which considers the long-term exposure rate of AEs was lower for those with previous exposure to leniolisib (3.3) compared to those with previous exposure to placebo (4.9).[38] Despite a large number of infections being reported as AEs across Study 2201 and Study 2201E1, in the OLE, 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), as described in Section B.2.6.3.

At least one AE was experienced by four participants (66.7%, [4/6]) in Study 2201 Part I, with a higher number of AEs noted in the highest dose of leniolisib compared with the lower doses (70 mg bid [66.7%, 4/6], 30 mg bid [33.3%, 2/6], 10 mg bid [33.3%, 2/6]).[44] Of the AEs experienced by participants in Study 2201 Part I, no clear trends were observed regarding the types of AEs reported, however, the most affected system organ class was infections and infestations (66.7%, [4/6]) [as in Study 2201 Part II and Study 2201E1] and respiratory, thoracic and mediastinal disorders (33.33%, [2/6]).[44]

As shown in Figure 19, across the three leniolisib clinical trials, 82.0% (433/528) of the AE/TEAEs reported by participants who were administered leniolisib were Grade 1–2.[38]

Severity of AEs/TEAEs

Of the 92 AEs reported with leniolisib treatment in Study 2201 Part II, the majority were mild to moderate in severity, Grades 1–2 (91.3%, [84/92]); AEs reported as Grades 1–2 were comparable between the treatment groups. In Study 2201 Part II, 19.0% (4/21) of participants in the leniolisib group experienced Grades 3–5 AEs, compared with 50% (5/10) in the placebo group.[17, 37]

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In the second interim analysis of Study 2201E1, with up to six years of available data, 79.4% (332/418) of TEAEs were mild to moderate in severity, Grades 1–2. Only one incidence of a Grade 5 TEAE was reported in Study 2201E1 which is described in Section B.2.10.5.[38]

In Study 2201 Part I, 17/18 AEs reported in the four participants were mild to moderate in severity, Grades 1–2, with no reports of Grade 4 or 5 AEs.[44]

The disaggregation of the varying AE/TEAE severities for participants across Study 2201 and Study 2201E1 is displayed in Appendix F.

B.2.10.4 Serious AE (SAEs)

All SAEs (defined as AEs which were fatal or life-threatening, resulted in persistent/significant disability, required inpatient hospitalisation or were medically significant) reported throughout Study 2201 Part I and Part II, and Study 2201E1, were assessed by the investigator as being unrelated to study treatment (Table 36).[17, 35, 38, 44, 255, 259]

Only Study 2201 Part II reported any SAEs; 20.0% (2/10) participants in the placebo group reported a total of six SAEs, whereas 14.3% (3/21) participants treated with leniolisib reported a total of five SAEs.(Table 36).[17] A Grade 5 SAE due to pulmonary hypertension was reported in one participant in the placebo group (10%, [1/10]) approximately 3.5 months after the final dose of study medication.[37] None of the SAEs reported were suspected to be related to leniolisib treatment.[17]

In Study 2201E1, 21.6% (8/37) of participants experienced 36 treatment-emergent SAEs, with less SAEs occurring in participants with previous exposure to leniolisib (19.2%, [5/26]: eleven events) than participants with previous exposure to placebo (33.3%, [3/9]: 25 events).[38] The most frequently affected system organ class for SAEs in Study 2201E1 was infections and infestations (13.5%, [5/37]; three participants had prior exposure to leniolisib and two participants had prior exposure to placebo) and gastrointestinal disorders (8.1%, [3/37]; all participants had prior exposure to leniolisib). The most common SAEs by preferred term were abdominal pain and pneumonia in 5.4% [2/37] participants overall.[38]

Dosing of leniolisib was temporarily interrupted in three participants (of which one had previous exposure to leniolisib) in Study 2201E1 due to SAEs. None of the SAEs reported in Study 2201E1 were considered by the investigator to be related to leniolisib treatment.[35, 38]

B.2.10.5 AEs/TEAEs leading to discontinuation or death

In Study 2201 Part I and Part II, none of the AEs led to discontinuation of leniolisib and no deaths were reported during the study period.[17, 27, 37, 44] In Study 2201E1, one participant (previous placebo) discontinued leniolisib treatment in Week 118 (Extension Day 826),[38] due to a diagnosis of Hodgkin's disease (SAE), which was considered unrelated to the study drug.[38, 285-287]

Overall, in the leniolisib clinical trials, two deaths have occurred:

- In Study 2201 Part II, a participant who received the placebo died due to pulmonary hypertension approximately 3.5 months after the final dose of study medication. This participant had not enrolled in Study 2201E1, and the death was deemed unrelated to the study treatment.[271]
- In Study 2201E1, one participant (2.7%) who had prior exposure to leniolisib reported an SAE of cardiac arrest, leading to the discontinuation of the study drug on Week 125 (Extension Day 878), and death a day later. This participant had a long history of various

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baseline co-morbidities including (but not limited to) cardiomyopathy, recurrent pneumonia, liver disease, and bronchiectasis. This SAE was considered unrelated to the study drug by the investigator (Table 37).[35, 38]

In the global EAP, as of 24th April 2024, three out of 72 individuals with APDS have discontinued leniolisib treatment, as a result of undergoing HSCT, being lost to follow-up due to relocation and one death (individual developed Hodgkin's lymphoma before discontinuing treatment).[263] The onset of malignancy and death was considered unrelated to leniolisib treatment.[43]

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Table 37. AEs/TEAEs leading to discontinuation or death in Study 2201 and Study 2201E1 (safety analysis set)

	Study 2201 Part I			Study 2201 Part II		Study 2201E1 (leniolisib 70 mg bid)			Total Leniolisib N=38 nE, nS (%)
	Leniolisib 10 mg bid N=6 nE, nS (%)	Leniolisib 30 mg bid N=6 nE, nS (%)	Leniolisib 70 mg bid N=6 nE, nS (%)	Leniolisib 70 mg bid n=21 nE, nS (%)	Placebo bid n=10 nE, nS (%)	Previous Leniolisib n=26 nE, nS (%)	Previous Placebo n=9 nE, nS (%)	Total Extension N=37 nE, nS (%)	
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (3.8)	1, 1 (11.1)	2, 2 (5.4)	2, 2 (5.3)
Study drug-related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to study withdrawal	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (3.8)	1, 1 (11.1)	2, 2 (5.4)	2, 2 (5.3)
Study drug-related AEs leading to study withdrawal	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

Footnotes: AEs or TEAEs have been classified according to the respective clinical study reports.
Abbreviations: AE: adverse event; bid: Bis In Die (twice daily); N: number of participants studied; nE: number of AE events in the category; nS: number of participants with at least one AE in the category; TEAE: treatment-emergent adverse event.
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 12).[38]

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B.2.10.6 Study drug-related AEs/TEAEs

During Study 2201 Part II, the incidence of treatment-related AEs were comparable between the two treatment groups (23.8%, [5/21] in leniolisib group compared to 30.0%, [3/10] in placebo group) [Table 38];[17] all AEs considered related to treatment in Part II were mild in severity. Treatment-related AEs by preferred term during Study 2201 Part II for leniolisib included aphthous ulcer (3.2%, [1/31]), taste disorder (3.2%, [1/31]), alopecia (6.5%, [2/31]), fatigue (3.2%, [1/31]), vomiting (3.2%, [1/31]) and headache (3.2%, [1/31]).[17, 37] No study-drug related AEs were reported in Study 2201 Part I.[44]

Infrequent treatment-related TEAEs occurred during Study 2201E1; five out of 37 participants (13.5%) experienced seven study drug-related TEAEs (Table 38). Of the participants who had prior exposure to leniolisib, 11.5% (3/26) experienced four treatment-related TEAEs compared to participants with previous exposure to placebo, whereby 11.1% (1/9) experienced two treatment-related TEAEs. Weight gain increase was the most frequently reported treatment-related TEAE, reported by 8.1% (3/37) of all individuals with APDS in Study 2201E1.[38]

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Table 38. Incidence of study drug-related AEs by preferred term in Study 2201 and Study 2201E1 (safety analysis set)

	Study 2201 Part I			Study 2201 Part II		Study 2201E1 (leniolisib 70 mg bid)			Total Leniolisib N=38 n (%)
	Leniolisib 10 mg bid N=6 n (%)	Leniolisib 30 mg bid N=6 n (%)	Leniolisib 70 mg bid N=6 n (%)	Leniolisib 70 mg bid n=21 n (%)	Placebo bid n=10 n (%)	Previous Leniolisib n=26 n (%)	Previous Placebo n=9 n (%)	Total Extension N=37 n (%)	
Participants with at least one AE	0 (0.0)	0 (0.0)	0 (0.0)	5 (23.8)	3 (30.0)	3 (11.5)	1 (11.1)	5 (13.5)	9 (23.7)
Preferred term									
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	2 (7.7)	1 (11.1)	3 (8.1)	4 (10.5)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.3)
Aphthous ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.6)
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.7)	1 (2.6)
Neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.7)	1 (2.6)
Taste disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vasculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Footnotes: A patient with multiple AEs within a dose/study part is counted only once in the 'at least one AE' row. A patient with multiple AEs within a dose/study part with the same preferred term is counted only once for that preferred term. Arranged in descending order of frequency (in Total leniolisib group) and alphabetically by preferred term.
Abbreviations: AE: adverse events; bid: Bis In Die (twice daily).
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 12).[38]

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B.2.11 Ongoing studies

Study 2201E1 commenced on 8th September 2016, with ongoing data collection on the long-term safety and efficacy of leniolisib. Results from the second interim analysis (DCO: 13th March 2023) are provided within this submission.[35, 38, 46] No further data cuts are currently anticipated from Study 2201E1 prior to study closure.

With respect to other data sources, Pharming has submitted a manuscript regarding the updated analysis of individuals with APDS within the ESID registry dataset (anticipated submission: Q1 2024). A publication on the UKPID registry is also planned, however, the UKPID registry is a major contributor of participants in the ESID registry.[6, 13, 43, 65, 66] It is anticipated that any new data are unlikely to change the conclusions presented in the evidence submission.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Principal findings of the clinical evidence base for leniolisib

The efficacy and safety of leniolisib for the treatment of individuals with APDS has been explored comprehensively in an international clinical trial programme. This included a successful, placebo-controlled, triple-blinded RCT (Study 2201 Part II) assessing leniolisib for the treatment of APDS versus placebo (in combination with selected symptomatic treatments). Further evidence is provided by a single-arm within-participant, dose-escalation trial, Study 2201 Part I, and an ongoing long-term extension, Study 2201E1.[17, 27, 35, 38] In addition, 72 individuals with APDS have received leniolisib in a real-world setting as part of Pharming's EAP, including six individuals in the UK across three centres.[43] As such, findings from the EAP, as well as real-world evidence from the ESID registry (externally controlled indirect matched comparisons), the NIH cohort and various case studies have been presented throughout the submission.[64, 252, 262]

There are currently no licensed treatments available for APDS in the UK. Consequently, individuals receive multiple symptomatic treatments in an attempt to manage individual manifestations, and the combination of immune dysregulation and immune deficiency.[3, 13, 14, 17, 18, 27, 28] Despite current management, individuals with APDS continue to experience disease progression and life-threatening manifestations, resulting in a reduced life expectancy compared with people without APDS.[12, 13, 15, 18] Additionally, the manifestations and treatments of APDS continue to substantially negatively impact HRQoL and daily living.[4, 11, 23] This highlights a clear unmet need for a generally well tolerated, licensed disease-modifying treatment that targets the underlying hyperactive PI3Kδ enzyme complex,[167] addressing the range of manifestations leading to improvements in HRQoL and mortality.

By targeting the hyperactive PI3Kδ pathway, treatment with leniolisib of individuals with APDS met both co-primary efficacy endpoints in Study 2201 Part II. This included a **statistically significant increase in the percentage of naïve B cells out of total B cells** versus placebo (see Section B.2.6.1), alongside **statistically significant improvements in lymphadenopathy** versus placebo (see Section B.2.6.2),[17] indicating immunophenotype normalisation and a reduction in lymphoproliferation; these results were maintained throughout Study 2201E1.[35, 38]

The evidence presented within this submission demonstrates that leniolisib provides long-term benefits to people with APDS across a wide range of clinically- and patient-relevant endpoints. Treatment with leniolisib results in long-term clinically meaningful benefits, such as a reduction in infections, improvement in cytopenia and gastrointestinal manifestations, reduced use or

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cessation of IRT accompanied by no increase in antibiotic use, prevention of manifestation progression (e.g. bronchiectasis), as well as improvements in HRQoL. In addition, no new study drug-related malignancies were observed during the leniolisib clinical trials and there has been no recurrence of lymphoma in participants with a history of lymphoma.[17, 27, 35, 38]

Leniolisib was generally well tolerated in Study 2201 Part I and Part II, with an overall AE profile comparable to placebo; leniolisib remained generally well tolerated with long-term therapy during Study 2201E1. Across the leniolisib clinical trials, most AE/TEAEs experienced by participants who were administered leniolisib were mild or moderate in severity, with low proportions of participants experiencing serious AE/TEAEs; none of the AEs/TEAEs reported that led to discontinuation or death were determined to be study drug-related.[17, 27, 35, 38]

Ultimately, leniolisib addresses the unmet needs in APDS, as it targets the underlying pathophysiology and ameliorates both the immune dysregulation and immune deficiency observed in individuals with APDS. In turn this is expected to lead to a reduction and cessation in the use of supportive medications, as well as long-term improvements in HRQoL and substantially reduced mortality.

Applicability to the decision problem

The clinical evidence presented within this submission has been derived from a SLR and further targeted searches of clinical evidence on the efficacy and safety of treatment options for APDS. The results of Study 2201 and Study 2201E1 represent the primary sources of clinical evidence for leniolisib as a treatment for APDS,[17, 27, 35, 38] and are relevant to the decision problem specified in the NICE final scope (see Table 1 in Section B.1.1).

Strengths of the clinical evidence base

Study 2201 (Part I and Part II) and Study 2201E1 provide relevant and robust data for the efficacy and safety of leniolisib for the treatment of adults and adolescents 12 years and older with APDS, with results generalisable to UK clinical practice:[17, 27, 35, 38]

- A strength of the leniolisib trials is their size relative to the overall APDS population. Considering APDS is an ultra-rare IEI, a substantial proportion of the diagnosed global population totalling 31 participants was recruited in the placebo-controlled, superiority trial, Study 2201 Part II, the largest known RCT in individuals with APDS. Across Study 2201 and Study 2201E1 a total of 38 individuals with APDS received leniolisib treatment
- Overall, both studies were considered to be of high quality with a low risk of bias, confirming their internal validity; moreover, in Study 2201 Part II, randomisation was adequate and triple blinding was applied
- For Study 2201 and Study 2201E1, a wide range of efficacy endpoints were selected for their clinical relevance, based on the hallmark clinical manifestations of APDS (see Section B.1.4.2), in addition to their patient-relevance (see ‘Clinical manifestations and impact on patient HRQoL’ for further detail)
- The results of the three leniolisib trials were aligned on the efficacy and safety of leniolisib for the treatment of APDS, demonstrating their validity and confirming the efficacy of leniolisib. Furthermore, findings from Study 2201E1 show that the benefits of leniolisib are maintained into the long-term
- In addition, further supplemental data from the EAP (where 72 individuals with APDS have received leniolisib) are presented throughout the submission, representing a larger sample size of individuals with APDS globally.[43] The results from the EAP support and validate the

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findings from the clinical trial programme, demonstrating that the outcomes seen in the trials are similarly observed in real-world clinical practice (see Section B.2.6.8)

The population enrolled within the leniolisib clinical trials can be considered comparable to the people who would receive leniolisib in UK clinical practice, making the results from these trials generalisable to UK clinical practice, for the following reasons:

- The leniolisib clinical trials enrolled a wide range of participants with study centre locations spanning across seven European countries, the United States of America and the Russian Federation,[37, 38, 44] all of which are anticipated to have similar demographics to the UK population (as described in Section B.2.3.2); the generalisability of the population was further supported by clinical opinion[14]
- The inclusion criteria permitted the enrolled trial populations to be aligned with the anticipated population of individuals with APDS who would be prescribed leniolisib in the clinical practice (see Section B.2.3.2). In Exercise 3 of the Expert Consultancy, all five clinicians agreed that the inclusion criteria reflect almost all participants that would receive leniolisib in the UK under its currently expected indication[14]
- As discussed in Section B.2.3.3, selected concomitant treatments including antibiotics and IRT were permitted during the leniolisib trials. The studies did not permit recent prior or concurrent use of immunosuppressive therapies (see Section B.2.3.1 for further detail), and no participants included in the leniolisib clinical trials had a medical history of HSCT.[17, 35, 43, 44] However, in Exercise 3 of the Expert Consultancy, at least four of the five clinicians agreed they would not prescribe each of sirolimus (loading and maintenance doses), rituximab, mycophenolate mofetil or cyclosporin alongside a PI3Kδ inhibitor;[14] therefore, the concomitant medication in the clinical trials is generally reflective of how leniolisib would be used in clinical practice. Externally controlled indirect matched comparisons showed statistically significant improvements in IgM levels and respiratory infection rates with leniolisib versus current clinical management including immunosuppressive therapies and with and without censoring people who had undergone HSCT.[262] Additionally, the benefit of leniolisib treatment has been demonstrated in one individual in clinical practice who experienced unsuccessful HSCT[260]

Limitations of the clinical evidence base

- It is acknowledged that the sample sizes of the leniolisib trials may have led to uncertainty in the interpretation of the results, as is common in ultra-rare diseases. This uncertainty was mitigated by providing supplemental and validatory evidence from the global EAP, case studies, as well as conducting externally controlled indirect comparisons with the data from the ESID registry, collecting expert insights and conducting supplemental analyses with real-world data from the NIH cohort[64, 252, 262, 266]
- The duration of the pivotal RCT, Study 2201 Part II, was 12 weeks, as restrictions on the use of immunosuppressants were applied meaning that a longer trial duration was considered unethical. However, published literature and findings from Study 2201 Part I indicated that a 12-week period was sufficient to assess the co-primary endpoints in Study 2201 Part II.[44, 255-257] Study 2201E1 provides long-term safety and efficacy data, providing data on important patient-relevant benefits such as infection rates and use of antibiotics and IRT (despite there being no procedure for reducing utilisation of concomitant medications in the trial protocols[43]), as well as supporting conclusions from Study 2201.[35, 38] Surrogate endpoint exploration analyses revealed that 12-week reductions in the proportion of transitional B cell and senescent CD8+ T cell levels (as percentages of total B and T cells,

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respectively) were associated with long-term improvements in PtGA, and that 12-week reductions in SPD index lesions were associated with long-term improvements in SF-36.[270] As noted above, the leniolisib clinical trials captured clinically and nominally significant benefit across a range of endpoints relevant to people with APDS (as informed by clinicians through expert insight exercises),[14] which is expected to translate into long-term benefits for these individuals

- In the absence of disease-specific HRQoL instruments that would be designed to be sensitive to the impact of APDS on HRQoL, SF-36 assessments were chosen to provide a broad picture of the impact of APDS and leniolisib treatment on all aspects of HRQoL, including physical functioning and the impact of APDS on everyday life. As SF-36 is a generic measure, the instrument may not have sufficiently captured the HRQoL changes in the APDS population, which is a common observation in rare diseases. Therefore, findings for SF-36 measurements were supported by PtGA scores and participant narratives which were collected during Study 2201 Part I and Part II, providing further insights into the perspectives of participants[17, 27, 35, 38, 64]

Conclusion

Study 2201 Part II was a robust, multicentre, placebo-controlled study which provided direct, clinical evidence for the efficacy and safety of leniolisib versus placebo in a substantial proportion of the diagnosed APDS population aged 12 years and older. Evidence from Study 2201E1 demonstrate that results are maintained long-term, with a total of 38 people with APDS being treated with leniolisib overall alongside selected concomitant treatments. Safety data suggest that leniolisib was generally well tolerated by participants in Study 2201, with an AE profile comparable to placebo; leniolisib remained generally well tolerated with long-term therapy during Study 2201E1. The leniolisib clinical trials were of high quality and provided evidence in alignment with the NICE final scope and generalisable to UK clinical practice.

With no other approved treatment options currently addressing the underlying cause of APDS, leniolisib is the first and only targeted therapy for individuals with APDS, selectively inhibiting p110δ in the hyperactive PI3Kδ enzyme complex. By normalising the PI3Kδ pathway, 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, all of which is expected to substantially reduce mortality and improve HRQoL (including improving an individual's energy levels and ability to complete daily activities, as well as restore their hope and general wellbeing). Together, the clinical evidence in this submission supports the durable efficacy and safety of leniolisib and its ability to fulfil the unmet need of a targeted therapy for treating APDS in people 12 years and over.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A de novo health state transition model was developed to evaluate the cost-effectiveness of leniolisib versus current clinical management in adults or adolescents with APDS aged 12 years or older, in line with the final scope from NICE for this evaluation. The cost-utility analysis adopted a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and health effects were discounted at annual rates of 3.5% and 1.5%,

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respectively, as leniolisib is expected to be prescribed from age 12 years and is expected to provide substantial and sustained benefits to the quality and length of life of people with APDS.

- The model consisted of two arms: the leniolisib arm had three mutually exclusive health states (alive on leniolisib treatment, alive not on leniolisib treatment, and death) and the current clinical management arm had two mutually exclusive health states (alive not on leniolisib treatment and death).
- APDS is a progressive disease; individuals with APDS experience an increasing number and increasing severity of manifestations over time.[10, 13, 18, 106] Within the alive health states, the model tracked the proportions of people with certain manifestations and receiving certain treatments at any given age, to capture the lived experience of individuals with APDS. Each manifestation and treatment were associated with cost and utility impacts, where appropriate. Individuals therefore accrued costs and QALYs as they experienced manifestations and received treatments over a lifetime horizon. Individuals could move from alive health states into death states at any point according to APDS-specific mortality.
- The age-specific incidence/prevalence of manifestations, and age-specific proportions of individuals receiving different treatments, under current clinical management, were largely based on data from the ESID APDS registry. Mortality was informed by the most recent and comprehensive known analysis of overall survival in APDS.[117]
- The impact of leniolisib on manifestations, treatment usage and survival was informed by a collective body of evidence, including Study 2201, Study 2201E1, the global EAP for leniolisib and results of a modified SEE conducted as part of the Expert Consultancy project (Exercise 1).
- In consideration of NICE's hierarchy of preferred HRQoL methods, utility data were informed by:
    - Proxy conditions, with validation during the Expert Consultancy, where possible, that the manifestation has a similar impact in the source condition as it does in APDS;
    - Valuation of vignettes by clinicians experienced in treating immunodeficiencies using EQ-5D-5L.
- Treatment-related disutilities for current clinical management options, capturing HRQoL impacts due to AEs and inconvenience, are included within the model. Adverse events are not explicitly modelled within the economic analysis, based on the similar rate of AEs between leniolisib and placebo in Study 2201 Part II, and the low expected cost of treating these AEs.
- Costs and healthcare resource use (HCRU) captured in the analysis included drug acquisition and administration costs, costs of treating manifestations as well as follow-up and monitoring costs. Costs and HCRU inputs were sourced from appropriate sources, including BNF, eMIT, other published sources and results from the quantitative survey of the Expert Consultancy (Exercise 4). Where required, the costs were inflated to 2022 GBP using the NHS cost inflation index.

Summary of the cost-effectiveness results

The results of the base case cost-effectiveness analysis demonstrate that leniolisib (with proposed PAS) is associated with increased health benefits versus current clinical management over a lifetime horizon, and was found to be plausibly cost-effective compared with current clinical management at a willingness-to-pay threshold of £100,000/QALY, yielding an ICER of £[redacted]/QALY. Results of scenario analyses showed that the base case ICER was

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robust to various data sources and assumptions around model inputs. Additionally, in the probabilistic sensitivity analysis (PSA), leniolisib had a [redacted]% chance of remaining cost-effective at a willingness to pay threshold of £100,000 weighted QALY gained. Given that clinical trial data, real-world evidence and modified SEE data were generalisable to UK clinical practice, as well as the validation of the modelling approach by clinical experts in the UK and the use of UK cost and resource inputs, the model and its results are considered to be reliable and generalisable to clinical practice in England.

B.3.1 Published cost-effectiveness studies

An SLR and subsequent update were conducted on 11th November 2021 and 18th May 2023, respectively, to identify published economic evidence, including economic evaluations and cost/HCRU studies, in people with APDS and their caregivers. The SLR had a broad scope, considering all people with APDS and their caregivers, with no restrictions placed on interventions, comparators or study location. This broad scope was maintained to ensure that no potentially relevant publications were missed in this ultra-rare, recently described disease.[1, 2] As the SLR was conducted more than six months prior to this evidence submission, supplementary targeted searches were completed on 9th April 2024.

The SLR and targeted searching did not identify any relevant economic evaluations in people with APDS. Full details of the methodology and results of the SLR are presented in Appendix G.

B.3.2 Economic analysis

As no cost-effectiveness models were identified by the economic evaluations SLR (see Section B.3.1), a de novo economic model relevant to the decision problem for this evaluation was developed.

B.3.2.1 Patient population

In line with the final scope for this evaluation, the anticipated licensed indication for leniolisib in the UK, and the population included in the leniolisib clinical trials (see Section B.2.3 for further details), this cost-effectiveness analysis considered adults and adolescents with APDS 12 years of age or older.

B.3.2.2 Model structure

Modelling approach

The de novo model evaluating the cost-effectiveness of leniolisib versus current clinical management was a health state transition model, consisting of three mutually exclusive health states (Figure 20):

- Alive on leniolisib treatment
- Alive **not** on leniolisib treatment (i.e. on current clinical management)
- Death

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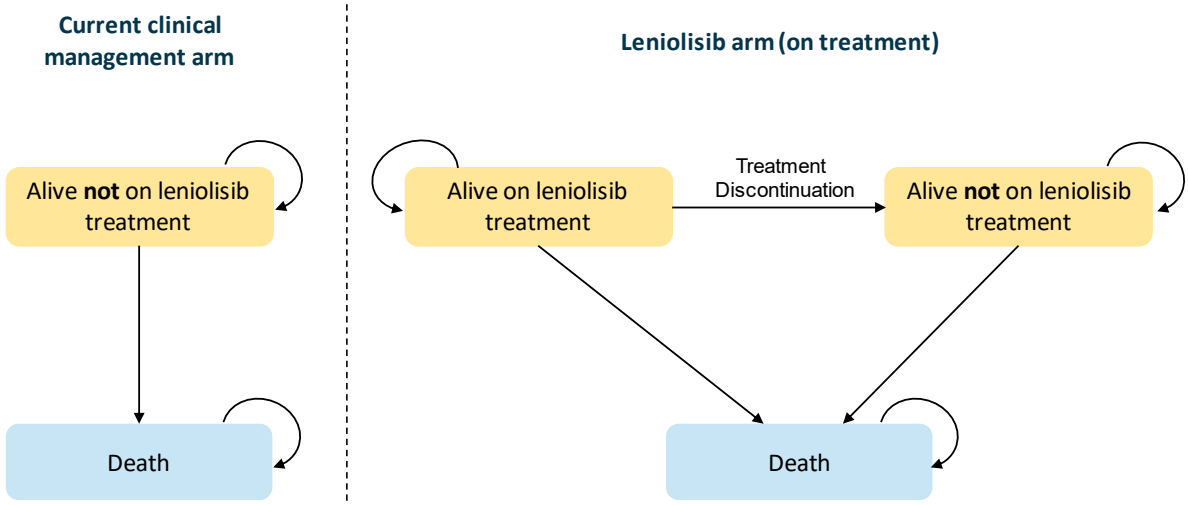
Figure 20. Model schematic



Individuals in the leniolisib arm entered the model on leniolisib treatment ("alive on leniolisib treatment") and remained so unless they discontinued treatment (see Section B.3.3.6), at which point they transitioned to the "alive not on leniolisib treatment" state. Individuals in the comparator arm entered the model directly into the "alive not on leniolisib treatment" state. Individuals in any "alive" state were permitted to transition to the deceased state, based on overall cycle-specific probabilities of mortality (see Section B.3.3.3).

Within each alive health state, the manifestation prevalence and treatment utilisation were estimated using a partitioned approach. The rates of manifestation and treatment use with leniolisib and current clinical management are described in Sections B.3.3.2 and B.3.3.3. Costs and utilities were calculated in each cycle based on manifestations and treatments and were accrued from model entry over a lifetime horizon to obtain estimates of total population costs and benefits in the leniolisib and current clinical management arms. Therefore, the benefits of leniolisib were modelled via reduced incidence and severity of manifestations, resolution of manifestations and reduced utilisation of treatments.

Justification for model structure

Various model structures were considered at the conceptualisation stage. The final model structure was chosen to reflect key characteristics of APDS and data availability, and was validated by three HTA experts and one UK clinical expert (see Section B.3.13), described below, and underwent conceptual validation via one-to-one interviews with three HTA experts representing Europe and Canada, as well as one UK clinical expert (see Section B.3.13 for further detail).

Progressive nature of APDS

As described in Section B.1.4.2, APDS is a progressive disease with heterogeneous presentation in which different manifestations first present at different ages throughout an individual's lifetime.[13, 16, 24, 106] The manifestation profiles of individuals with APDS are therefore age-dependent, and disease progression is characterised by the accumulation of multiple manifestations, which impact patient HRQoL and health care system costs to varying degrees, over time. The chosen model structure allows the model to track the average age-dependent onset of multiple, key manifestations at a cohort level, in line with the progressive nature of APDS.

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An alternative approach modelling disease progression via movement through health states based on disease status or response was not considered feasible:

- A model structure consisting of health states based on disease status (complete response, partial response, no response, worsening or death) was explored. However, there is no definition of response in treatment guidelines for APDS, reflective of the recent recognition and ultra-rare nature of the condition.[1, 2, 162] Furthermore, APDS is a multi-system disease, and response is likely to be patient-specific given their symptoms
- Improvements in the co-primary endpoints of Study 2201 Part II have been correlated with improvements in manifestations such as rates of respiratory infections,[270] but identifying correlations is not possible across the full range of APDS manifestations. Fewer than 100 patients were identified globally at the time Study 2201 began,[44] and the knowledge of APDS was incomplete. As a result, defining response criteria using data from Study 2201 was not possible, due to a relatively small sample size and the heterogeneity in manifestations experienced
- In the leniolisib clinical trial programme, there was no discontinuation due to lack of treatment response. Additionally, in the Expert Consultancy project, clinicians did not anticipate that patients would discontinue leniolisib based on lack of response,[14] therefore rendering a 'no response' health state meaningless

Overlap in manifestations

As described in Section B.1.4.2, people with APDS experience differing combinations of manifestations across multiple organ systems, leading to cumulative HRQoL impacts (as demonstrated by the results of vignette studies [see Section B.3.4.5]),[4, 7, 13, 110] as well as accumulation of cost impacts associated with the management of multiple manifestations. The chosen model structure with simply defined "alive" health states allowed flexibility for individuals occupying each health state to experience differing combinations of concomitant manifestations, in line with the natural history of APDS.

Alternative model structures were considered:

- A series of mutually exclusive health states describing individual manifestations would limit the ability of the model to capture the characteristic overlap in manifestations experienced by people with APDS. A large number of health states would be needed, requiring an even larger number of transition probabilities to be calculated; in an ultra-rare disease such as APDS, it would be highly challenging to calculate accurate and reliable transition probabilities for a large number of health states
- Defining model health states based on common, mutually exclusive combinations of manifestations was considered infeasible, as available data from the ESID registry show that people with APDS experience diverse combinations of manifestations (i.e., common combinations could not be found)

Overlap in treatment use

Acute antimicrobials are prescribed to treat acute infections.[3] Contrastingly, some treatments are prescribed to manage multiple manifestations of APDS, such as the use of IRT to reduce the risk of infections and to manage autoimmune cytopenias (such as thrombocytopenic purpura [high doses of IRT required]).[43, 178, 181] Individuals with APDS also typically require several concomitant medications, as described in Section B.1.4.3.[3, 13, 28] Considering the complexity of concomitant treatment use, and the lack of UK treatment guidelines for APDS, it is not always feasible to delineate a precise link between the occurrence of a single manifestation and usage of different

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treatments. The chosen model structure allowed the model to capture expected usage rates for both those treatments linked to single manifestations and those prescribed to manage multiple manifestations, in addition to the overlap in treatment usage.

Availability of data

As has been described throughout this submission, APDS is an ultra-rare disease that was first recognised in 2013.[2] Therefore, as is common in ultra-rare diseases, availability of data on manifestation rates, treatment use and mortality was considered during model conceptualisation. The model structure was chosen in consideration of available data from the ESID registry[16, 66, 72, 302] and Hanson and Bonnen, 2024.[19]

Previous models in other disease areas

No published economic models in APDS were identified by the economic evaluations SLR (Section B.3.1). However, the design challenges described above are present for a number of other diseases, which have been modelled using a similar approach to the current economic model. The Sheffield Type 1 Diabetes Policy Model used sub-models to determine prevalence of multiple specific manifestations/conditions affecting distinct organ systems before consolidating cost and utility information per cycle.[303] A sub-model approach was also used in HST14 for evaluation of metreleptin, where each manifestation was modelled separately and then mortality, cost, and utility estimates were calculated in each cycle as a result.[304]

Conclusion

Overall, a simple cohort model with each manifestation and treatment modelled with a partitioned approach was deemed the most appropriate approach to accurately capture key aspects of APDS, notably:

- the progressive nature of APDS, characterised by age-dependent onset of manifestations
- the complex overlap in manifestations experienced across distinct organ systems
- the use of diverse, concomitant treatments to address individual manifestations or combinations of manifestations

Choice of manifestations and treatments

The economic model included the following manifestations.

- lymphoproliferation (including splenomegaly)
- cytopenia (including neutropenia, anaemia and thrombocytopenia)
- gastrointestinal manifestations
- malignancies (including but not limited to lymphoma)
- infections (all types)
- hearing loss
- bronchiectasis-associated airway disease
- advanced lung disease

The model also included the following treatments:

- IRT
- antimicrobial therapies (antibiotics, antifungals and antivirals)
- immunosuppressive therapies
- HSCT

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- Tonsillectomies (representing surgical interventions)

These manifestations and treatments were chosen to allow the model to best capture how leniolisib would impact the lived experience of patients with APDS and costs to the NHS, compared to current clinical management alone, as they:

- have been commonly reported within published literature, registry analyses and interviews,[6, 12, 13, 16, 18, 23] and/or
- negatively impact the HRQoL and daily lives of patients, from their perspectives (see Section B.1.4.2 for further detail),[11, 23, 38] and/or
- impact the survival of people with APDS,[19, 117] and/or
- incur treatment costs to the NHS (see Section B.1.4.5), and/or
- are expected to be impacted by leniolisib treatment (based on overall conclusions of the clinical trials, real-world evidence and Expert Consultancy project)[14, 17, 26, 27, 35, 263, 266]

Additionally, the chosen treatments are representative of those used to manage the complex manifestations experienced by individuals with APDS according to UK clinicians.[14]

Clinical experts identified tonsillectomy, adenoidectomy, lymph node excision/biopsy, splenectomy, incision and drainage of abscess, sinus surgery and bronchoscopy as the surgical interventions commonly used in APDS.[14] However, Kaplan Meier (KM) curves could only be constructed for data on tonsillectomy from the ESID registry;[16, 66, 72, 302] therefore, the cumulative incidence curve for tonsillectomy was included in the model.

Summary and key features of the base case economic model

Key features of the base case economic analysis and their justifications are summarised in Table 3.

Table 3. Key features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Lifetime horizon (85 years)	In line with the NICE reference case. Leniolisib generally expected to be taken lifelong after treatment initiation; a lifetime horizon allows all relevant costs and benefits to be captured.
Cycle length	Annual cycles (with a half-cycle correction)	Year-long cycles were considered adequate to capture the rate of disease progression and align with the frequency of data collection in the ESID registry. A half-cycle correction was employed to adjust for the distribution of costs and benefits accrued throughout each cycle.
Treatment waning effect	Not included	Due to the mechanism of action of leniolisib (Section B.1.2), a treatment waning effect was not expected. Furthermore, no evidence of treatment waning has been observed in the leniolisib clinical trials, with up to six years of data from Study 2201E1 available.[38]
Source of manifestation and treatment rates	• ESID registry and Study 2201 Part II (for the current clinical management arm) • Study 2201, Study	Please refer to Section B.3.3.2 for further detail and justification.

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	2201E1, EAP survey and Expert Consultancy (for the impact of leniolisib vs current clinical management)	
Source of utilities	Proxy conditions, as reported in scientific literature, and vignette study	The sources for utilities included in the model and justification for choice has been captured in Section B.3.4.
Source of costs	Various sources, including but not limited to NHS reference costs, BNF 2023 and the Expert Consultancy	UK costs were prioritised where possible. The sources for all relevant costs have been summarised and justified in Section B.3.5.
Discount rate	• 3.5% per annum for costs • 1.5% per annum for health effects	As discussed in Section B.1.4.2, individuals with APDS can experience severe and often persistent manifestations occurring early in life and over their lifetime, which have a substantial negative impact on HRQoL.[4, 7, 13, 110] In addition, the length of life for individuals with APDS is significantly shortened.[19, 117] As detailed in Section B.2.6:[14, 17, 27, 35, 37, 38, 263, 305] • Leniolisib normalises immunophenotype, including returning B and T cells to normal ranges and allowing reduction in or cessation of IRT use • Leniolisib provides improvements across a wide range of manifestations which all individually decrease HRQoL and shorten life • Therefore, leniolisib is expected to substantially extend and improve the quality of life for these people who may otherwise have severely impaired quality and length of life • Additionally, in the EAP, rates of hospitalisations due to infections and other APDS complications decreased by >80% after initiation of leniolisib treatment. As part of the Expert Consultancy project (Exercise 4, quantitative), clinical experts estimated considerable decreases in the frequency of specialist visits for patients receiving leniolisib versus those receiving standard of care • Overall, through its disease-modifying mechanism of action (rather than treating individual symptoms), treatment with leniolisib is expected to lead to a substantial reduction in healthcare resource utilisation and a reduced need for treatments typically associated with complications and disease progression over time. This is likely to result in long-term cost savings for the NHS • There are no treatment-related deaths reported in the clinical trials and EAP Leniolisib treatment is expected to be commenced early in life, at age 12 (or upon diagnosis if this occurs after the age of 12 years). With clinical trial data

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		available for up to six years, there is no evidence of treatment waning, so the benefits of leniolisib are expected to be sustained lifelong.[38] Therefore, to avoid a large reduction in the value of health benefits that occur in the long-term for these young individuals with APDS, a 1.5% annual discount rate for health effects was used. Costs were discounted at 3.5% per annum for consistency across NICE evaluations.
Perspective	NHS/PSS in England	In line with the NICE reference case.

Abbreviations: TA: technology appraisal.
Source: Harrington et al., 2023,[117] Maccari et al., 2023,[13] Study 2201 Part II CSR Version 2.0, Novartis 2020,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38] Rao et al., 2017,[27] Rao et al., 2023,[17] Rao et al., 2023[35] and The Balancing Act, 2023.[26]

B.3.2.3 Intervention technology and comparators

Intervention: leniolisib

The dose of leniolisib incorporated into the economic model was 70 mg bid for all cycles, in line with the anticipated marketing authorisation, and the dose received in the pivotal RCT (Study 2201 Part II) and the ongoing long-term extension (Study 2201E1).[17, 35] It is anticipated that leniolisib will be used after APDS diagnosis in individuals aged 12 years and older (Section B.1.4.3).

Comparator: current clinical management

In line with the final scope for this evaluation, the cost-effectiveness analysis compared leniolisib to current clinical management in the UK, as represented by the treatments described in Section B.1.4.3.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline age

Leniolisib is anticipated to be licensed as a treatment for APDS in adults and adolescents 12 years of age or older. However, the model was run for a cohort of individuals starting treatment at age 15, which is the average age of people with APDS in the Level 1 (mandatory) dataset of the ESID registry (November 2023 dataset).[16, 66, 72, 302] Thus, the baseline age of the population in the economic model was aligned with that of the ESID registry, and therefore, is expected to align with clinical practice in the UK.

B.3.3.2 Current clinical management: manifestation rates and treatment use

In the base case economic analysis, the age-specific manifestation rates in the current clinical management arm were informed by the cohort of individuals with APDS in the ESID registry (DCO: November 2023),[16, 66, 72, 302] for the following manifestations:

- lymphoproliferation (including splenomegaly)
- cytopenia (including neutropenia, anaemia and thrombocytopenia)
- gastrointestinal manifestations

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- malignancies (including but not limited to lymphoma)
- bronchiectasis-associated airway disease
- advanced lung disease

Prior to analysis of the ESID registry data, the dataset was prepared as detailed in the associated report.[16] As part of the modified SEE during the Expert Consultancy project (Exercise 1), clinical experts were provided with evidence, including cumulative incidence plots (derived from KM data), to indicate the incidence of APDS manifestations from sources such as the ESID registry. They were then asked to provide lower and upper plausible estimates for the proportion of patients with APDS with each manifestation at multiple timepoints on current clinical management. Means were calculated for the group lower and upper plausibility estimates for each manifestation at each age. The rates of all manifestations at each age from the ESID registry fell between the clinicians' lower and upper plausibility estimates, providing validation of the manifestation rate data from the ESID registry used in the economic model.[14]

The rates of occurrence of infections and hearing loss under current clinical management were informed by data from Study 2201 Part II:

- Whilst the proportion of individuals (receiving current clinical management) with infections was informed by cumulative incidence data from the ESID registry, the annual number of infections was obtained from the annualised rate of infections in the placebo arm of Study 2201 Part II up to Week 12, 3.476 (SE: 1.56).[17, 38] This is a conservative estimate; during the modified SEE of the Expert Consultancy project (Exercise 1), clinicians estimated that individuals suffer from 6.88 (SD: 2.61) respiratory infections and 3.60 (SD: 2.78) infections of other types year[14]
- The ESID registry does not report on any individuals with APDS with hearing loss (only reported as "unknown" or "no").[16] However, the literature (Section B.1.4.2) and interviews with patients revealed that hearing loss is often experienced by patients with APDS.[11, 12, 23] The age-specific rates of hearing loss in the economic model were obtained from the medical history dataset of Study 2201 Part II.

KM curves displaying the manifestation rates informing the current clinical management arm of the economic model are presented in Figure 21; the numerical data informing these curves (incidence and cumulative incidence) are available within the economic model.

With regards to treatment use rates within the economic model:

- Each episode of acute infection incurred acute use of antimicrobials (a weighted average of antibiotic, antiviral and antifungal use; see Section B.3.5.1 for further information)
- It was assumed that prophylactic antimicrobial treatment would be received by most individuals with a history of infection; therefore, prophylactic antimicrobial use was linked to the cumulative rate of infections from the ESID registry
- Rates of use of all other treatments (IRT, immunosuppressive therapies, HSCT and tonsillectomies) were informed by the APDS cohort in the ESID registry. The rates of use of these treatments were not linked to individual manifestation rates, as they are each prescribed to address multiple manifestations, as described in Section B.1.4.3. This approach of modelling treatment use independently of manifestation rates prevented double counting of treatment use

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Cumulative incidence plots (derived from KM data) displaying the treatment use rates (excluding antimicrobials, which are linked to infection rates) informing the current clinical management arm of the economic model are presented in Figure 22.

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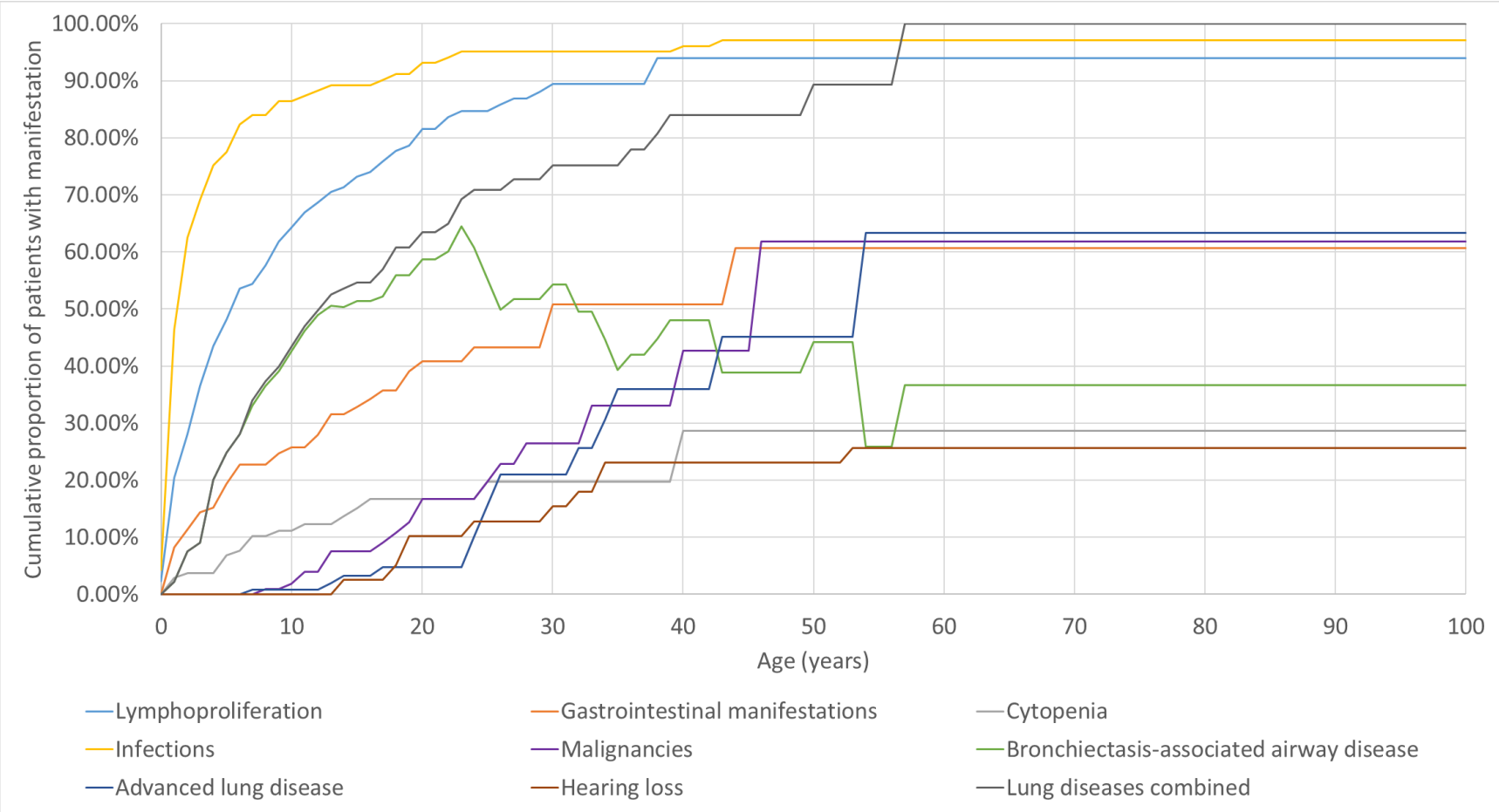
Figure 21. Cumulative incidence of (proportions of people with APDS with) manifestations in the base case economic model



Footnotes: Advanced lung disease is a subset of bronchiectasis-associated airways disease; therefore, to prevent double counting of costs and utility impacts in the economic model, the cumulative proportion of individuals with advanced lung disease was calculated by subtracting the proportion with bronchiectasis-associated airway disease from the total proportion with 'lung disease combined'. This allowed manifestations to be mutually exclusive in the economic model. Therefore, the proportion with bronchiectasis-associated airway disease decreases with increasing age, as patients progress to develop advanced lung disease. 'Lung disease combined' is shown for information only, and does not represent a manifestation included in the model.
Abbreviations: APDS: activated PI3K delta syndrome, ESID: European Society for Immunodeficiencies.
Source: ESID Registry,[66] Study 2201 Part II CSR Version 2.0, Novartis 2022[37] and Rao et al., 2023.[17]

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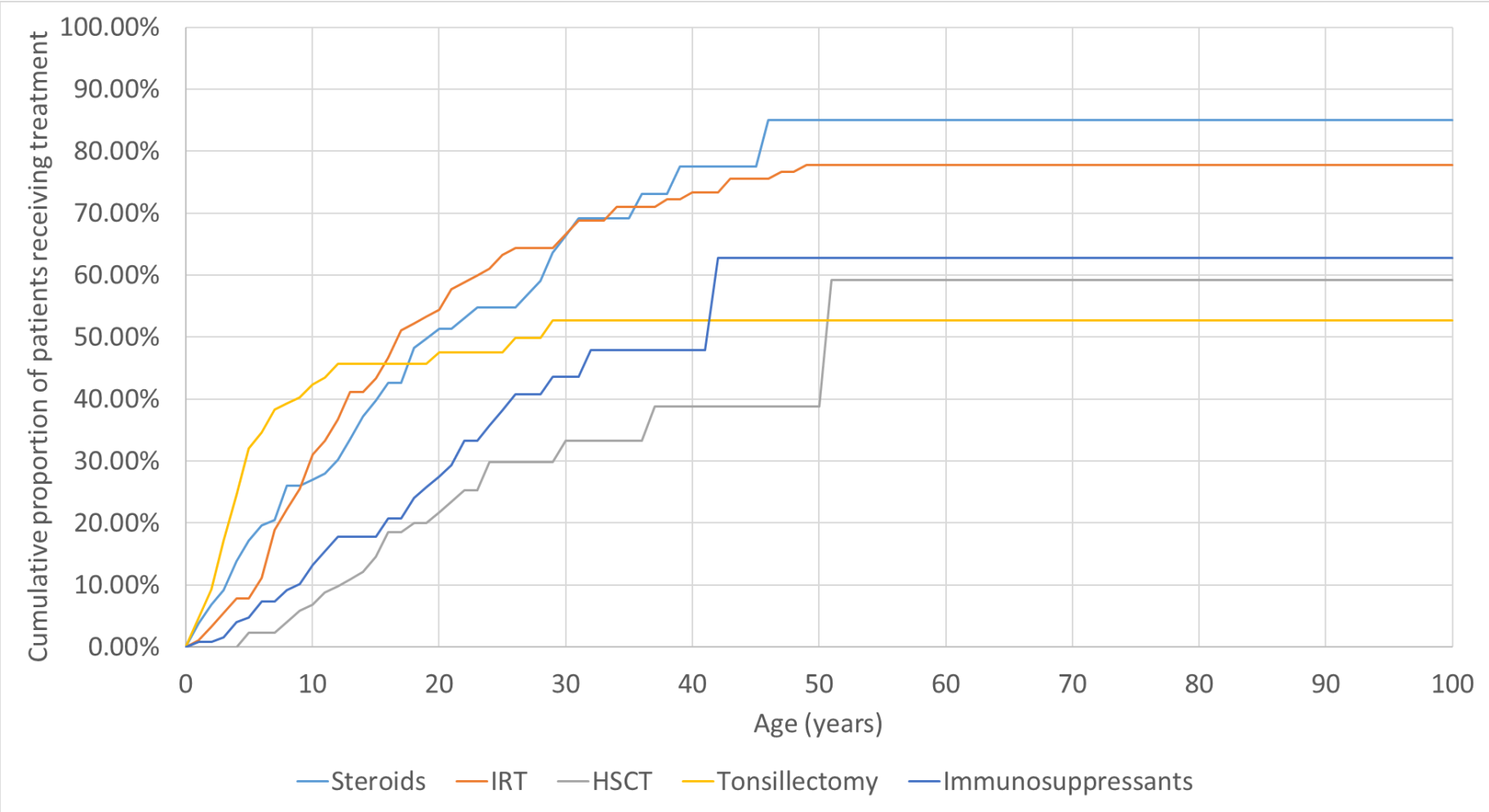
Figure 22. Cumulative incidence of (proportions of people with APDS with) treatment use, excluding antimicrobials, in the base case economic model



Abbreviations: APDS: activated PI3K delta syndrome, HSCT: haemopoietic stem cell transplantation, IRT: immunoglobulin replacement therapy, ESID: European Society for Immunodeficiencies.
Source: ESID Registry.[66]

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B.3.3.3 Current clinical management: overall survival

Overall survival (i.e., transitions from the alive state to the death state) in the current clinical management arm of the economic model was informed by a Weibull curve fitted to KM data from the Pharming case series of individuals with APDS. This is described further below.

Hanson and Bonnen, 2024, conducted an SLR identifying cases of APDS for a survival analysis.[19] An update of this SLR was conducted by Pharming, which generated a case series of 351 unique individuals with APDS of which 41 had died, from 108 eligible publications, referred to as the "Pharming case series".[117] The resultant patient-level data from the case series were used to construct a KM curve of overall survival among people with APDS (Figure 3). Based on the company's understanding, this dataset presents the most comprehensive estimate of overall survival amongst individuals with APDS being treated with current clinical management. However, the review may be biased towards reporting information from surviving patients, so the use of this dataset forms a conservative approach.

Selection of the base case parametric model for overall survival of individuals with APDS was based on standard criteria:

- Visual inspection of goodness of fit to observed KM data: during the modified SEE conducted as part of the Expert Consultancy project (Exercise 1), clinicians were presented with an overall survival KM curve constructed from the original dataset by Hanson and Bonnen, 2022 (the pre-print of Hanson and Bonnen, 2024, reporting the results of the original SLR).[306] A simple, monotonic hazard underlay the overall survival KM curve by Hanson and Bonnen, 2022; therefore, three monotonic curves were fitted (over a lifetime horizon), overlaid onto the KM data and presented to clinicians: exponential (hazard function remains constant over time), Weibull (hazard function decreases monotonically) and Gompertz (hazard function only increases or decreases monotonically). Complex accelerated failure time models (log-normal, log-logistic and generalised gamma) were not considered in order to minimise the complexity of the exercise. Clinicians were asked to indicate whether they thought the presented fitted curves were clinically plausible, and if yes, to rank the fitted curves by their clinical plausibility. The clinicians' preferred curve for overall survival was the Weibull curve[14]
- Objective statistical measures of goodness of fit to observed KM data: Akaike information criterion (AIC) and Bayesian information criterion (BIC) were also considered. Out of the three fitted curves presented to clinicians, the Weibull curve was associated with the median AIC and BIC (see Table 39)

Table 39. Parametric curve fit for overall survival, based on the Hanson and Bonnen, 2022 dataset

Parametric model	AIC	BIC
Exponential	347.6184177	351.1278061
Gompertz	340.283269	347.3020456
Weibull	336.4793648	343.4981415

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Given the above, the base case parametric model chosen for overall survival was the Weibull curve. A Weibull curve was subsequently fitted to the Pharming case series dataset, which is the update of the Hanson and Bonnen dataset, given that it is a more recent analysis with a greater number of identified individuals with APDS included in the dataset.[117, 306] As part of the modified SEE during the Expert Consultancy project (Exercise 1), clinical experts were asked to provide

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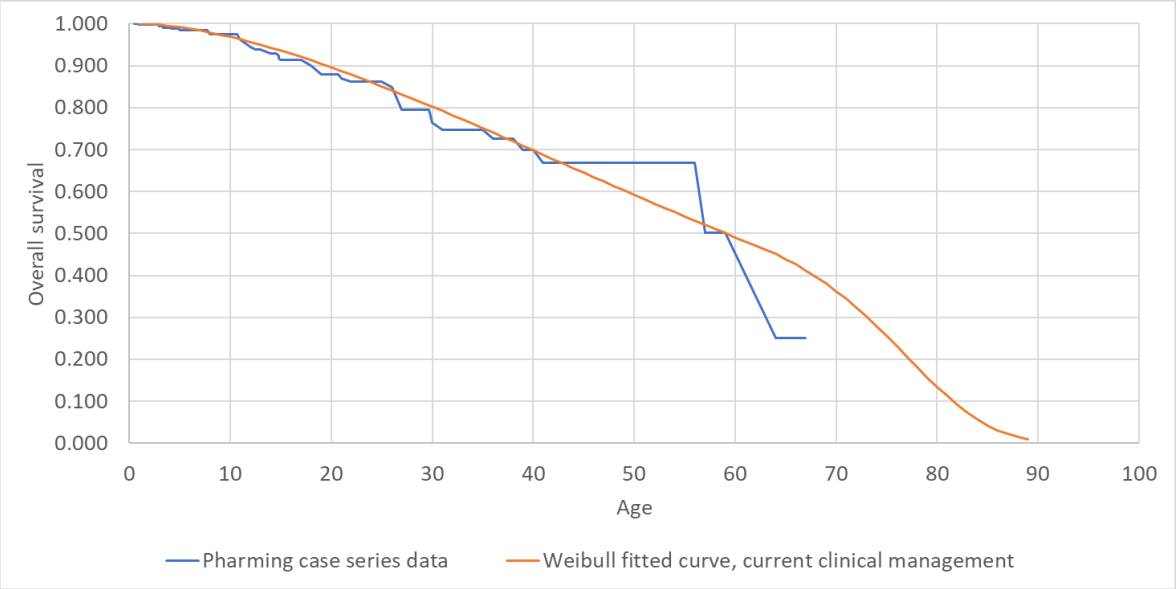
lower and upper plausible estimates for the proportion of patients with APDS that would be expected to be alive at ages 12, 30 and 45 on current clinical management, after viewing the Hanson and Bonnen dataset.[14, 306] Overall survival at each age from the Pharming case series dataset fell between the clinicians' lower and upper plausibility estimates. Therefore, the Pharming case series dataset can be considered similar to the Hanson and Bonnen dataset, and it is expected that the results of the goodness of fit assessment described above would carry over to the Pharming case series dataset.[14, 117, 306] AIC and BIC for the parametric curves fitted to the Pharming case series dataset are presented in Table 40, with the Weibull curve overlaid onto the Pharming case series KM curve displayed in Figure 23. The Weibull curve is still associated with the lowest AIC and BIC compared with the other simple monotonic parametric curves, indicating its goodness of fit to the Pharming case series dataset.

Table 40. Parametric curve fit to overall survival data from the Pharming case series dataset, used in the economic model

Parametric model	AIC	BIC
Exponential	481.5000	485.3411
Gompertz	471.3000	478.9765
Weibull	466.8000	474.4326

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

Figure 23. General population capped survival of individuals with APDS



Abbreviations: APDS: activated PI3K delta syndrome.

Of note, it was assumed that people with APDS could never experience mortality hazards lower than the general population (informed by National Life Tables for England, 2018–2020),[307] as a patient with no complications would have a similar risk of death to that of the general population. All analyses were conducted using R® version 4.2.2. The package "flexsurv" was used for parametric survival analysis.

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B.3.3.4 Impact of leniolisib

Impact of leniolisib on manifestations

Overview

A collective body of evidence on the benefit of leniolisib treatment was considered, following the hierarchy presented in Table 41, in order to robustly model the impact of leniolisib on APDS manifestations.

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Table 41: Hierarchy of clinical evidence sources considered for the economic model

Hierarchy level	Evidence source	Description
1 (highest priority)	Leniolisib clinical trials	Post hoc responder analyses of Study 2201 Part II and Study 2201E1 were performed based on thresholds of clinically meaningful response for selected manifestations elicited via a Delphi panel with 24 clinicians with experience in managing individuals with APDS or PID.[39, 266, 276] Methodology is reported in Section B.2.4.2, and results throughout Section B.2.6.
2	Leniolisib EAP	As detailed in Section B.2.3.4, Pharming have established a global EAP, which provides individuals with APDS who were unable to enrol within the clinical trial programme an opportunity to be treated with leniolisib. Further details are presented in Section B.2.3.1, and results throughout Section B.2.6.
3 (lowest priority)	Modified SEE (Expert Consultancy Exercise 1)	As part of Exercise 1 of the Expert Consultancy project, clinicians were supplied with an evidence package, including cumulative incidence plots (derived from KM data) to indicate the incidence of APDS manifestations from sources such as the ESID registry. The clinical experts were then asked to provide upper and lower plausible estimates for the following:[14] • The incidence of the applicable clinical manifestations at specified ages in individuals receiving current clinical management (Exercise 1, Part 1) • The incidence of the applicable clinical manifestations at specified ages, after initiation of leniolisib at ages 12 or 20 (Exercise 1, Part 2) For current clinical management (Exercise 1 Part 1) and for leniolisib (Exercise 1 Part 2), midpoints of the mean lower and upper plausible estimates provided by clinicians were calculated, at the specified ages. Based on these midpoints, hazard ratios (HR) were calculated to estimate the impact of leniolisib on the **incidence** of each manifestation, at the specified ages. For each manifestation, an average HR value was calculated from the HRs for each age. These HRs were applied to the age-specific ESID manifestation rates, in order to estimate age-specific manifestation incidence rates with leniolisib, for use in the model.[14] In order to elicit evidence on the reduction in the **severity** of manifestations with leniolisib treatment, clinicians were asked to estimate the proportions of patients aged 12 and over who were expected to experience improvement, with regards to HRQoL, in applicable clinical manifestations after three years of receiving leniolisib (Exercise 1, Part 2). A time-point of three years was chosen as this is the time expected to be required for immune system reconstitution.[280, 281] The midpoint of the aggregated lower and upper plausible estimates provided by clinical experts for the proportions of people with APDS who would experience improvement after three years of receiving leniolisib was calculated for each applicable manifestation.[14] Please refer to the Expert Consultancy report for further details on the methodology.[14]

Abbreviations: APDS: activated PI3Kδ syndrome; ESID: European Society for Immunodeficiencies; HR: hazard ratio; HRQoL: health-related quality of life; PID: primary immunodeficiencies.
Source: Ogonek et al., 2016,[281] Pharming Data on File, 2023[14] and van der Maas et al., 2019.[280]

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The following benefits with leniolisib treatment have been observed in the clinical trial programme and/or EAP (Section B.2.6) or have been predicted in the modified SEE (Expert Consultancy Exercise 1; see below),[14, 17, 27, 35, 38, 263] and have hence been modelled in the economic analysis:

- Reduction in the **incidence** (i.e. the rate of new cases of each manifestation) of all manifestations to varying degrees, beyond the first year of treatment;
- **Resolution** (i.e. complete alleviation in terms of impact on HRQoL and resource use) of certain manifestations in the first year of leniolisib treatment and beyond, in varying proportions of patients who were already experiencing the manifestation on current clinical management;
- **Reduction in severity** or improvement (in the impact on HRQoL and resource use) for certain manifestations in the first year of leniolisib treatment and beyond, in varying proportions of patients who were already experiencing the manifestation on current clinical management. A 50% reduction in the costs and utility impacts associated with manifestations was applied for individuals experiencing a reduction in the severity of the manifestation, based on the results of the Expert Consultancy (see Sections B.3.4.5 and B.3.5.2);
- **No change** (in the impact of HRQoL and resource use) for certain manifestations in the first year of leniolisib treatment and beyond, in varying proportions of patients who were already experiencing the manifestations on current clinical management.

The base case clinical inputs for the impact of leniolisib on each manifestation are described below.

Lymphoproliferation

Table 42: Impact of leniolisib on lymphoproliferation in the economic model

Lymphoproliferation	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	0.42	N/A	96%
Source	Study 2201E1 and EAP[263]	N/A	Study 2201E1 responder analysis[276]
Justification	• The annual hazard of developing lymphoproliferation is 3.8% under current clinical management, using an exponential parametric fit to the KM curve for overall lymphoproliferation from the APDS cohort aged 12 to 57 (the observation with the maximum age) in the ESID registry • The annual hazard of developing new lymphoproliferation when receiving leniolisib is estimated to be approximately 1.6%, based on 1 event in 60.5 patient-years of follow-up:	• Refer to Table 25 in Section B.2.6.2 for the Study 2201E1 responder analysis, using the Delphi panel threshold • The Study 2201E1 responder analysis is consistent with the EAP survey data presented in Section B.2.6.8 The economic model did not differentiate between the reduction in severity and the resolution of lymphoproliferation. Clinical opinion indicates that individuals experiencing improvement in lymphoproliferation will no longer experience the HRQoL impact associated with lymphoproliferation.[14] Additionally, during the validation of the modified SEE results, a clinical expert	

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	○ In Study 2201E1, 1 of 37 patients developed new lymphoproliferation by Day 252[38] ○ In the EAP survey, new or worsening lymphoproliferation was reported for 0 out of the 29 patients with approximately 14 months of follow-up on average[263] • Therefore, HR=0.42 for the incidence of lymphoproliferation with leniolisib versus current clinical management • In the modified SEE of the Expert Consultancy (Exercise 1), the estimated HR was 0.31; therefore, the base case value of 0.42 represents a conservative HR[14]	highlighted that improvement in lymphoproliferation as seen with leniolisib treatment could be regarded as symptomatic resolution, consequently mitigating any further impact on HRQoL.[14] Finally, the response threshold from the Delphi panel used in the Study 2201E1 responder analysis for the percentage reduction in spleen volume leading to a notable increase in patients' HRQoL is similar to that used for treatment response (and utility gain) for splenomegaly in the proxy condition of myelofibrosis (Section B.3.4.3).[308]

Abbreviations: APDS: activated PI3Kδ syndrome; EAP: early access programme; HR: hazard ratio; HRQoL: health-related quality of life; KM: Kaplan-Meier SEE: structured expert elicitation.

Cytopenia

Table 43: Impact of leniolisib on cytopenia in the economic model

Cytopenia	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	0	N/A	78%
Source	Modified SEE (Expert Consultancy, Exercise 1)[14]	N/A	Study 2201E1 responder analysis[39]
Justification	• The annual hazard of developing cytopenia is 1% under current clinical management, using an exponential parametric fit to the KM curve for antibody-mediated autoimmunity from the APDS cohort aged 12 to 57 (the observation with the maximum age) in the ESID registry • The annual hazard of developing new cytopenia when receiving leniolisib is estimated to be approximately 0.7%, based on 1 event over 147 patient-years of follow-up: ○ In Study 2201E1, 0 of 37 participants developed new cytopenia during a mean of 159.76 weeks of follow-up[263]	• Refer to Table 27 in Section B.2.6.2 for the Study 2201E1 responder analysis, using the Delphi panel threshold[276] • The Study 2201E1 responder analysis is consistent with the EAP survey data presented in Section B.2.6.8, which showed 80% of patients experiencing total remission or meaningful improvement[276] The economic model did not differentiate between the reduction in severity and the resolution of cytopenia. Within the proxy condition for cytopenia (immune thrombocytopenic purpura [ITP], Section B.3.4.3), treatment response, and consequently improved HRQoL, is characterised by achieving normal platelet levels without the need for	

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	○ In the EAP survey, one new case of anaemia was reported amongst 30 patients with a mean follow-up of approximately 14 months (Table 33)[263] • This suggests HR=0.64 for the incidence of cytopenia with leniolisib versus current clinical management • However, both the clinical trials and EAP survey observed high rates of cytopenia improvement with leniolisib (80% or more), indicating any new cytopenia is likely to be transient • Additionally, in the modified SEE of the Expert Consultancy (Exercise 1), clinicians indicated that leniolisib treatment could lead to zero new incidences of cytopenia (mean lower plausible estimate)[14] • Therefore, a HR of 0 was used in the base case	rescue medication. Notably, the Study 2201E1 data indicated no signs of rescue medication, with the majority of participants reaching normal levels of platelets.[35, 38] Therefore, it was concluded that all patients whose cytopenia responded to leniolisib treatment (per the Delphi panel responder thresholds) experienced resolution of cytopenia with regards to its HRQoL and cost impact.

Abbreviations: APDS: activated PI3Kδ syndrome; EAP: early access programme; HR: hazard ratio; HRQoL: health-related quality of life; KM: Kaplan-Meier SEE: structured expert elicitation.

Gastrointestinal manifestations

Table 44: Impact of leniolisib on gastrointestinal manifestations in the economic model

Gastrointestinal manifestations	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	0	78% (of those who did not show resolution)	36%
Source	EAP[263]	EAP[263]	EAP[263]
Justification	• GI manifestations were not measured in the leniolisib clinical trials • In the EAP survey, among patients without pre-existing GI manifestations (n=14), there were no new reports of GI manifestations. Amongst all patients in the EAP survey with responses to GI questions (n=28), 1 patient with colitis at baseline experienced a new colitis event during >2 years of treatment of leniolisib, as well as complete remission of baseline GI obstruction symptoms, and low body weight[263]	Refer to Table 33 in Section B.2.6.8 for the EAP survey data. • The model considers individuals without resolution separately to individuals with resolution. Therefore, the proportion of individuals with severity reduction was expressed as a proportion of those without resolution, i.e. the 50% of individuals with meaningful improvement and 14% with no change were weighted to 78% with meaningful improvement (severity reduction) and 22% with no change, so that these proportions added to 100%.	

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	• Therefore, a HR of 0 was used in the base case	

Abbreviations: APDS: activated PI3Kδ syndrome; EAP: early access programme; HR: hazard ratio; HRQoL: health-related quality of life; KM: Kaplan-Meier SEE: structured expert elicitation.

Infections

Study 2201E1 and Study 2201 Part II informed annualised infection rates with leniolisib and current clinical management, respectively, in the model (Table 45).[17, 35, 37, 38] As a conservative assumption, leniolisib was not modelled to resolve or reduce the severity of infections, only the incidence. For leniolisib, the infection rates observed in Year 4 of Study 22011 were assumed to remain constant in subsequent years.

Table 45. Annualised infection rates

Year	Current clinical management			Leniolisib		
	Mean	SE	Source	Mean	SE	Source
Year 1	3.476	1.56	Study 2201 Part II (Annualised rate of infections counted up to Day 84, in placebo arm)	1.962	0.38	Study 2201E1 (Annualised infection rate for individuals who have previously received leniolisib)
Year 2				1.474	0.29	
Year 3				0.923	0.43	
Year 4+				[redacted]	[redacted]	

Abbreviations: SE: standard error.
Sources: Study 2201 Part II CSR v2.0, Pharming Data on File, 2022,[37] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[38]

Hearing loss

Table 46: Impact of leniolisib on hearing loss in the economic model

Hearing loss	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	0.28	There are no data available on the reduction in severity of hearing loss with leniolisib, so this was conservatively not included in the model	Resolution not expected with leniolisib treatment
Source	Modified SEE (Expert Consultancy, Exercise 1)		
Justification	• In the qualitative survey of the Expert Consultancy (Exercise 3), clinicians indicated that a reduction in the incidence of infections would reduce the incidence of hearing loss in people with APDS[14] • Hearing loss was not measured as an efficacy outcome in the		

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	leniolisib clinical trials; there was one incidence of deafness (not study drug-related) in Study 2201 Part I however, there were no new incidences of deafness reported during Study 2201 Part II or Study 2201E1[38] • Moreover, in the EAP, there were no new events reported by physicians regarding hearing loss in individuals with APDS receiving leniolisib[263] • Results from the modified SEE (Expert Consultancy, Exercise 1) indicated that HR=0.28 for the incidence of hearing loss with leniolisib versus current clinical management		

Abbreviations: APDS: activated PI3Kδ syndrome; EAP: early access programme; HR: hazard ratio; SEE: structured expert elicitation.

Bronchiectasis-associated airway disease

Table 47: Impact of leniolisib on bronchiectasis-associated airway disease in the economic model

Bronchiectasis-associated airway disease	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	0.28	33% (of those without resolution)	10%
Source	Study 2201E1/EAP	EAP	EAP
Justification	• The annual hazard of developing bronchiectasis-associated airway disease is 0.024 under current clinical management, using an exponential distribution fit to the KM curve for bronchiectasis from the APDS cohort aged ≥12 years in the ESID registry • The annual hazard of developing bronchiectasis-associated airway disease when receiving leniolisib is estimated to be 0.007. There were no cases of new bronchiectasis or bronchiectasis progression over 121.7 patient-years of follow-up in Study 2201, and only one new case of bronchiectasis over 30.25 patient-years of follow-up in the EAP survey:[263] ○ In Study 2201, no new infective exacerbations of bronchiectasis were observed in participants without bronchiectasis at Baseline,[37] over 68.8	Refer to Table 33 in Section B.2.6.8 for the EAP survey data • Three individuals had missing values in the EAP survey, meaning that 10% showed resolution when using complete data • The proportion with severity reduction was expressed as a proportion of those without resolution (as explained in Table 44)	

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	patient-years of follow-up (for patients without bronchiectasis at baseline only) ○ Post hoc analyses of lung imaging data in Study 2201E1 (for 14 participants) confirms no progression of bronchiectasis, with improvement observed in some patients[263] ○ In the EAP survey, for patients without bronchiectasis at Baseline (n=17), one individual had a new event of bronchiectasis[64] • Therefore, a HR of 0.28 was used in the base case	

Abbreviations: EAP: early access programme; ESID: European Society for Immunodeficiencies; HR: hazard ratio; KM: Kaplan-Meier.

Advanced lung disease

Table 48: Impact of leniolisib on advanced lung disease in the economic model

Advanced lung disease	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	0	100%	Resolution not expected with leniolisib treatment
Source	Study 2201E1/EAP	EAP	
Justification	• In Study 2201, there were no new events of advanced lung disease progression[263] • In the EAP survey, there were no new events of progressive lung disease or other serious pulmonary manifestations during leniolisib treatment[64] • Therefore, a HR of 0 was in the base case • Additionally, in the qualitative survey of the Expert Consultancy (Exercise 3), one clinician noted that if leniolisib could reduce chronic infection and inflammation in the lungs, leniolisib treatment could slow or halt the progression of disease[14]	Refer to Table 33 in Section B.2.6.8 for the EAP survey data	

Abbreviations: EAP: early access programme; HR: hazard ratio.

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Malignancies

Table 49: Impact of leniolisib on malignancies in the economic model

Malignancies	Hazard ratio (incidence reduction)	Severity reduction	Resolution
Input	HR=0.55	Severity reduction not expected with leniolisib treatment	Resolution not expected with leniolisib treatment
Source	Study 2201E1/EAP		
Justification	• The annual risk of developing malignancy is 1.3% under current clinical management, using an exponential distribution fit to the KM curve for 'any malignancy' from the APDS cohort aged 12 to 57 (the observation with the maximum age) in the ESID registry • The annual probability of developing malignancy when receiving leniolisib is estimated to be approximately 0.7%, based on: ○ In Study 2201 and Study 2201E1, there has been one case of malignancy out of 38 participants (DCO: 13th March 2023),[17, 27, 35, 38] over 119.7 patient-years of follow-up ○ In the EAP, a new case of malignancy was reported out of 60 individuals,[64] over 102.5 patient-years of follow-up (as of 17 May 2024) ○ There have been no cases of malignancy for patients treated with commercial supply of leniolisib in the US or abroad (using commercial supply) over approximately 60 patient-years of follow-up[309] ○ Neither case of malignancy was associated with leniolisib[38, 43] • This suggests HR=0.55 for the incidence of malignancy with leniolisib versus current clinical management • Moreover, this HR is within the plausible range estimated during the modified SEE of the Expert Consultancy (Exercise 1)[14]		

Abbreviations: DCO: data cut-off; EAP: early access programme; ESID: European Society for Immunodeficiencies; HR: hazard ratio; KM: Kaplan-Meier.

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Impact of leniolisib on treatments

Antimicrobials

As described in Section B.3.3.2, the rates of acute and prophylactic antimicrobial use were linked to the rate of infections in the economic model. Therefore, reduced infection rate with leniolisib compared with current clinical management was linked to a concurrent reduction in the use of antimicrobial therapy.

Supportive of this approach, in the pivotal Study 2201 Part II and throughout Study 2201E1, the annualised rate of antibiotic usage was numerically lower in participants treated with leniolisib compared to in the placebo arm of Study 2201 Part II.[41, 42] In the quantitative survey conducted as part of the Expert Consultancy (Exercise 4), clinicians also estimated that use of acute and prophylactic antibiotics would decrease by 67% and 50%, respectively, upon initiation with a PI3Kδ-specific inhibitor (leniolisib).[14]

IRT

Intrapatient analysis of data from Study 2201E1 informed risk ratios for the reduction in IRT use with leniolisib treatment in the economic model (Table 50).[263] For example:

- At Study 2201E1 Baseline, 27/37 participants were using IRT;[17, 35] this proportion includes all participants at Baseline regardless of prior study drug, as the durations of Study 2201 Part I and Part II were not long enough for IRT use to decrease
- In Year 2, this proportion had dropped to 19/27 participants
- Therefore, the risk ratio for IRT use with leniolisib versus current clinical management in Year 2 was (19/27)/(27/37) = 0.96[38]

Immunosuppressive therapies

As part of the Expert Consultancy project (Exercise 4), clinicians were asked “by what % do you think use of immunosuppressives (excluding mTOR inhibitors) would be reduced by a PI3Kδ-specific inhibitor?”. The mean response was [redacted]; therefore, a risk ratio for leniolisib versus current clinical management of [redacted] was implemented in the economic model.[14] Given that steroids are usually taken lifelong after initiation in APDS, the impact of leniolisib on steroid use was modelled by applying a reduction to the cumulative rate of steroid use, before applying this reduced, constant rate of steroid use in the long-term (Table 50).

As part of the Expert Consultancy project (Exercise 3), the majority of clinicians responded that they would not consider use of any other immunosuppressive treatments alongside use of leniolisib in line with the clinical trials (such as rituximab or mTOR inhibitors; see report for further details).[14] Therefore, it was assumed for the economic model that patients receiving leniolisib did not use any immunosuppressive treatment, other than steroids.

Tonsillectomy

As leniolisib treatment reduces the incidence of infections, as well as the incidence and prevalence of lymphoproliferation, this is expected to reduce the need for surgical interventions (i.e. a reduction in incidence). As part of the quantitative exercise of the Expert Consultancy project (Exercise 4), clinicians were asked “By what % do you think the number of surgical procedures (to include tonsillectomy, splenectomy, lung transplant) required by individuals with APDS would be reduced by a PI3Kδ-specific inhibitor treatment?” The mean response across clinicians was 62.0% (please see report for further details).[14] Although clinicians were asked

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about tonsillectomy, splenectomy, lung transplant, cumulative incidence plots could only be constructed for data on tonsillectomy from the ESID registry; therefore, the incidence of tonsillectomy was included in the model. It was assumed that the value of 62.0% was applicable for tonsillectomy in the model. The impact of leniolisib tonsillectomy was modelled via a reduction in incident use of this one-off treatment.

HSCT

Leniolisib treatment is expected to lead to reductions in the incidence of lymphoma, prevention of the progression of manifestations and organ damage and reduced or stop use of current treatments, therefore reducing the need for HSCT.[14] Moreover, it was assumed that patients in the leniolisib arm of the model would not undergo HSCT; if HSCT were deemed appropriate, the patient first discontinues leniolisib treatment before receiving HSCT, as exemplified by one case in (Section B.2.10.5). Therefore, the model assumed no use of HSCT in the leniolisib arm.

Summary

Table 50 summarises the impact of leniolisib on treatment use in the "Alive on leniolisib treatment" state of the economic model.

Table 50. Impact of leniolisib on treatment use in the base case of the economic model ("Alive on leniolisib treatment" state)

Treatment		HR or RR	SE	Reduction modelled	Source
Antimicrobials		N/A		Linked to reduction in infection rate	Study 2201E1
IRT	Year 1	1.00	0.14	Reduce cumulative rate of use	Study 2201E1
	Year 2	0.96	0.16		
	Year 3	0.84	0.21		
	Year 4	0.86	0.29		
	Year 5	[redacted]	[redacted]		
Steroids		[redacted]	[redacted]	Reduce cumulative rate of use and keep constant	Expert Consultancy (Exercise 4)
Immunosuppressants		0.00	0.00	Reduce cumulative rate of use and keep constant	Expert Consultancy (Exercise 3)
HSCT		0.00[a]	0.00	Reduce incidence	Assumption, based on Study 2201E1/EAP experience
Tonsillectomy		0.38	0.04	Reduce incidence	Expert Consultancy (Exercise 4)

Footnotes: Individuals in the "Alive on leniolisib treatment" state had no risk of undergoing HSCT; the risk of HSCT for individuals who had taken leniolisib was captured in the cohort of individuals who discontinued treatment.
Abbreviations: HR: hazard ratio; HSCT: haematopoietic stem cell transplantation, IRT: immunoglobulin replacement therapy, RR: risk ratio.
Sources: Study 2201E1 CSR (IA2), Pharming Data on File, 2023,[38] and Pharming Data on File, 2023[14] and Pharming Data on File, 2024.[263]

Impact of leniolisib on survival

Given the short duration and small trial population size of Study 2201 Part II, a low number of mortality events was expected during the trial. As such, the effect of leniolisib on mortality was not assessed as a pre-specified efficacy endpoint in the trial. Therefore, during Part 2 of the

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modified SEE (Exercise 1 of the Expert Consultancy project), clinical experts were also asked to provide upper and lower plausible estimates for mortality at specified ages (ages 20 and 40 years) based on initiation of leniolisib at age 12 years.[14] A HR for survival of [redacted] (with SE assumed to be [redacted]) was estimated based on clinical expert opinion:

- The experts' plausible range for long-term survival after age 12 under current clinical management was used to calculate a cumulative hazard, which was then annualised, with a median of 0.0118. This is substantially lower than the mortality rate of 73.5% observed from age 12 to 67 in the Pharming case series data, which would indicate an annualised hazard of 0.0241. However, for consistency in the calculation and to provide a conservative estimate of survival gains for leniolisib, the expert opinion was used
- Expert commentary suggested the survival curve for leniolisib should be closer to that of the general population; each expert's upper plausible range for long-term survival on leniolisib treatment after age 12 was used to calculate a cumulative hazard, which was then annualised, with a median of [redacted]

Once individuals in the "Alive on leniolisib treatment" state of the model discontinue leniolisib treatment and enter the "Alive not on leniolisib treatment" state, their annual risk of mortality returns to that under current clinical management (Section B.3.3.3).

Figure 24: Overall survival in the base case economic model

B.3.3.5 Adverse events

As discussed in Section B.2.10, leniolisib was generally well-tolerated in Study 2201 Part I and Part II, with an overall AE profile comparable to placebo; leniolisib remained generally well-tolerated with long-term therapy during Study 2201E1.[17, 27, 35, 38] As demonstrated in Section B.2.10.6, similar treatment-related AEs were reported across the leniolisib and placebo treatment groups. In Study 2201 and Study 2201E1, 82.0% (433/528) AE/TEAEs reported by participants who were administered leniolisib were Grade 1 or Grade 2 and were therefore assumed to have minimal HRQoL impact and require no additional treatment. Furthermore, in Study 2201E1,

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TEAEs occurred infrequently in 13.5% (5/37) of individuals, of which none led to discontinuation of study treatment or study withdrawal.[17, 35, 38]

The impact of AEs on costs and HRQoL was therefore considered small and similar between treatment groups, and the inclusion of AEs in the economic model would not have had a substantial impact on the findings of the cost-effectiveness analysis. Therefore, AEs were not explicitly modelled within the economic analysis. However, treatment-related disutilities for current clinical management options, capturing HRQoL impacts due to treatment-related AEs and inconvenience, were included within the model, as described in Section B.3.4.5.

B.3.3.6 Treatment discontinuation

During a total follow-up of almost 200 patient-years of leniolisib exposure across Study 2201E1 and the EAP, 7 cases of leniolisib discontinuation have been reported (Table 51), giving a discontinuation rate of 3.54% per patient-year, informing the discontinuation rate in the base case of the economic model (i.e. transition from the "Alive on leniolisib treatment" state to the "Alive not on leniolisib treatment" state in the leniolisib arm of the economic model). No participants have discontinued due to lack of response to leniolisib.[263]

Table 51: Discontinuation data from Study 2201E1 and the leniolisib EAP

Programme	Number of discontinuations	Approx. total patient-years exposure	Reasons for discontinuation
Study 2201E1 (DCO: March 2023)[a]	4	122.3	• Death: n=1 • AE (Hodgkin's lymphoma): n=1 • Withdrawal: n=1 • Did not enrol in Study 2201E1 after completing Study 2201 Part II: n=1
EAP (as of 30 Jan 2024)	3	75.6	• Death: n=1 • HSCT: n=1 • Lost to follow-up (moved away from centre): n=1
Total	**7**	**197.9**	-

Footnotes: [a]Does not include two patients in Russia whose study site closed and subsequently enrolled in the EAP, death of one participant from the placebo arm of Study 2201 Part II before they could enrol into Study 2201E1, and one participant who completed six years of follow-up in Study 2201E1 and subsequently enrolled in the leniolisib EAP. Does include one patient who completed Study 2201 but did not enrol into Study 2201E1, which is not counted as a trial discontinuation in Section B.2.3.1.
Source: Pharming Data on File, 2024.[263]

It is uncertain how the rate of manifestations and treatment use would change upon discontinuation of leniolisib treatment. There is one report of an individual with a treatment gap of 15 months between Study 2201 Part I and Study 2201E1 whose spleen volume increased to a level as before starting treatment, which then reduced again after initiating treatment in Study 2201E1.[310] Other individuals with a treatment gap between Study 2201 Part I and Study 2201E1 also experienced increases in their IgM levels and decreases in naïve B cells, which improved after starting treatment again in Study 2201E1.[38, 310] Taking this and the mechanisms of action of leniolisib into account, it was assumed that individuals in the leniolisib arm of the economic model who discontinued leniolisib treatment (i.e. transitioned to the "Alive and not on leniolisib treatment" state) would experience an increased risk of manifestation occurrence, treatment use and mortality, rather than these rates remaining stable beyond leniolisib discontinuation.

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Given that changes to the constitution of the immune system may occur over a period of several years,[280, 281] it was assumed that for individuals discontinuing leniolisib treatment (i.e. entering the "Alive and not on leniolisib treatment" state), the cumulative proportions of patients experiencing manifestations or using treatments would increase over time to the levels in the current clinical management arm. Given the lack of data, it was assumed for simplicity that these would be linear increases for each manifestation or treatment, with the constant annual increases equivalent to the average annual incidence of each manifestation or treatment up to the age at which the last patient reported the incidence of the respective manifestation or treatment use in the ESID registry (Table 52).[66, 72, 302] For any given age, the economic model does not allow cumulative incidence to become higher than the standard care arm at the same age.

Assuming that the cumulative proportions of patients with manifestations or using treatments in individuals who discontinued leniolisib treatment immediately jumped to the proportions in the current clinical management arm would disregard the length of time which is required for reconstitution of the immune system. It would also require those who discontinued leniolisib treatment to experience a higher incidence of manifestations or treatment use in the "catch-up" period than those who have never received leniolisib. This approach would likely have overestimated the incidence of manifestations in the "Alive but not on leniolisib treatment" arm.

Table 52: Constant annual increase in the incidence of manifestations or treatment use in the "catch-up" period for individuals who discontinued leniolisib treatment in the economic model

Manifestation or treatment	Annual increase in occurrence or use
Lymphoproliferation	2.41%
Gastrointestinal manifestations	1.38%
Cytopenia	0.72%
Infections	2.16%
Malignancy	1.34%
Bronchiectasis-associated airway disease	1.75%
Advanced lung disease	1.17%
Hearing loss	0.48%
Steroids	1.85%
IRT	1.59%
HSCT	1.16%
Tonsillectomy	1.82%
Immunosuppressants	1.49%

Abbreviations: HSCT: haematopoietic stem cell transplantation; IRT: immunoglobulin replacement therapy.

B.3.4 Measurement and valuation of health effects

Summary

As described in Section B.1.4.2, available evidence shows that the impact of APDS on HRQoL increases as the number of manifestations experienced increases, and that current treatment options are associated with a high patient burden. In order to reflect the progressive and cumulative impact of APDS manifestations and treatments on HRQoL in the economic model:

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- Individuals in the model had an age-adjusted 'baseline' level of utility (i.e., the HRQoL of people with APDS experiencing no manifestations and treatments that were included in the model)
- As individuals experience various manifestations and receive associated treatments, utility impacts associated with individual manifestations and treatments were applied to the age-adjusted baseline utility values

In summary, and in consideration of NICE's hierarchy of preferred HRQoL methods:

- HRQoL data from the leniolisib clinical trials could not be used to inform baseline utility nor the utility impact of manifestations and treatments in the base case (Section B.3.4.1)
- No APDS-specific utility data were identified in the literature (Section B.3.4.3)
- Baseline utility and the utility impacts of manifestations and treatments were therefore sourced from (Section B.3.4.3):
    - A targeted search conducted to identify utility values associated with APDS manifestations and treatments from proxy conditions
    - 'Clinician EQ-5D vignette study', in which clinicians completed EQ-5D-5L based on a series of APDS health state vignettes[311]
- Base case utility values were informed by the proxy utility values and the clinician EQ-5D vignette study (the latter of which also provided validation of proxy literature values), due to the clinicians' expertise in managing people with immunodeficiencies with multiple manifestations
- A 'TTO vignette study', in which members of the general public valuated vignettes using TTO methods, generated utility impacts of manifestations that were generally aligned to the utility values from proxy conditions and the clinician EQ-5D vignette study[23]

The impact of leniolisib on HRQoL was captured via:

- Reductions in the rates of manifestations and treatment use with leniolisib treatment
- Where a reduction in the severity of manifestations was experienced with leniolisib treatment, the utility impact of the manifestation was reduced by 50%, based on the results of the Expert Consultancy (Section B.3.4.5)[14]
- A utility gain of 0.1, expected to capture the overall improvement in the wellbeing of patients associated treated with leniolisib, including increased vitality and reduced anxiety, and improvement in manifestations not captured within the economic model

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D was not measured in the leniolisib clinical trials; instead the SF-36 was used to evaluate participant HRQoL in Study 2201 and Study 2201E1 (see Section B.2.6.7).[17, 27, 37, 38] However, SF-36 data from the clinical trials could not be used to inform HRQoL in the base case of the economic model because:

- SF-36, being a generic measure, was not designed to capture the specific HRQoL benefits important for people with APDS, as evidenced by patient narratives. Additionally, it demonstrated a lack of sensitivity in detecting meaningful changes in certain domains of SF-36 (Section B.2.6.7)
- In order to enrol into Study 2201 and Study 2201E1, participants were required to have lymphoproliferation and a history of repeated oto-sino-pulmonary infections and/or organ dysfunction (Section B.2.3.1). Therefore, baseline SF-36 data from the clinical trials included the impact of lymphoproliferation and other manifestations on HRQoL, whereas

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only a proportion of patients in the model experienced each manifestation during each cycle. Using trial baseline SF-36 data to inform the baseline level of HRQoL in the model may therefore have overestimated the impact of APDS on HRQoL. Nevertheless, a scenario analysis was conducted using baseline SF-36 data from Study 2201 Part II[37]
- Stratification of the SF-36 results to provide utility data associated with individual manifestations and treatments was not possible due to the complex combinations of manifestations experienced, and treatments used, by each study participant

B.3.4.2 Mapping

HRQoL data from the clinical trials were not used in the base case economic analysis. Mapping of baseline SF-36 data from Study 2201 Part II to EQ-5D was conducted for a scenario analysis, described in Section B.3.10.3.

B.3.4.3 Health-related quality-of-life studies

Results of the systematic literature review

An SLR and further targeted searches were conducted to identify any published studies reporting on the HRQoL of individuals with APDS. Full details of the methodology and results of this SLR and targeted search are presented in Appendix H.

Only three relevant publications were identified by the HRQoL/utility SLR and further targeted searches:

- Rao et al., 2017, reporting on Study 2201 Part I, which reported PtGA values (presented in Section B.2.6.7)[27]
- Rao et al. 2023 and Rao et al. 2024,[35, 282] both reporting on Study 2201E1, which reported PtGA, SF-36 and WPAI
- To note, the clinical SLR identified Rao et al., 2023, reporting on Study 2201 Part II;[17] this was not identified by the HRQoL/utility SLR as the abstract of the publication did not mention HRQoL evidence.

HRQoL data from the above listed clinical trials were not suitable for use in the base case of the economic model, as discussed in Section B.3.4.1. Overall, no utility values in APDS were identified by the HRQoL/utility SLR.

Given the lack of utility data identified from the clinical trials and HRQoL/utility SLR, and in consideration of NICE's hierarchy of preferred HRQoL methods, the following exercises were conducted, described in the below subsections:

- A targeted search conducted to identify utility values associated with APDS manifestations and treatments from proxy conditions
- 'Clinician EQ-5D vignette study', in which clinicians completed EQ-5D-5L based on a series of APDS health state vignettes[311]
- 'TTO vignette study' in which members of the general public valuated vignettes using TTO methods[23]

Proxy utility values

To identify utility impacts associated with the various manifestations experienced and treatments used by individual with APDS, a targeted literature review was conducted. The first search

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primarily included IEIs that were most similar in clinical presentation to APDS. The conditions searched were those recommended by six global IEI experts, and included CVID with non-infectious complications, cytotoxic T-lymphocyte associated protein 4 deficiency, LPS responsive beige-like anchor protein deficiency, autoimmune lymphoproliferative syndrome, STAT3 gain-of-function disease and hyper IgM syndrome.[312]

Sufficient relevant data were not obtained via this first search. Therefore, the targeted search was subsequently broadened to include manifestation/treatment-specific search terms, regardless of the underlying condition. Further details of the study selection process, with the inclusion and exclusion criteria employed for both stages of this targeted literature review are provided in Appendix O. Prioritisation of proxy utility values for inclusion in the base case (Table 53) was based on a number of factors:

- Use of EQ-5D to estimate utility values; however, this was not always possible, forming a limitation of the approach
- Similarity of the clinical presentation in the proxy condition to APDS, to ensure generalisability of the utility values
- Use in previous NICE technology evaluations
- Validation of proxy conditions by clinicians in the qualitative survey conducted as part of the Expert Consultancy (Exercise 4).[14] In Table 53, "Proxy condition validated in Expert Consultancy project" means that clinicians agreed that the manifestation in the proxy condition has a similar HRQoL impact to the manifestation in APDS

EQ-5D vignette valuation

Alongside searching for proxy utility values, four clinicians (including two from the UK) completed the EQ-5D-5L (Proxy version #1) questionnaire based on a series of vignettes.[311]

Twelve health state vignettes were developed in line with DSU best practice recommendations and Matza et al., 2021,[313, 314] including incorporation of input from interviews with people with APDS, such that the vignettes incorporated the patient perspective. The vignettes comprised of a baseline health state, an "APDS general" state, and individual or combinations of manifestations experienced by individuals with APDS added to the baseline health state. The final vignettes are presented in Appendix M. EQ-5D-5L was completed by clinicians (rather than a sample of the general public or people with APDS), as many complex vignettes that reflected the realistic overlap in manifestations were included. The results obtained from EQ-5D-5L were cross-walked to the corresponding EQ-5D-3L utility values, through the use of the Hernandez Alava algorithm.[315] Please see the EQ-5D survey report for full details of the development and validation of the vignettes, valuation methods and results.[311]

Alongside the proxy utility values, utilities generated via the clinician EQ-5D vignette study informed the economic model in this submission and provided validation for the proxy utility values, given the clinicians' expertise in managing people with APDS and/or other immunodeficiencies and knowledge of the impact of multiple manifestations on HRQoL.

TTO vignette valuation

In addition to the clinician EQ-5D exercise, a set of the vignettes were separately valued by members of the general public using the TTO method. The TTO vignette study generated utility impacts of manifestations that were generally aligned to the utility values from proxy conditions and the clinician EQ-5D vignette study. The clinicians completing the EQ-5D vignette study had firsthand experience in treating individuals with APDS, giving them a deeper and more nuanced

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understanding of its impact on quality of life (QoL) than the general public. Therefore, utility values from the TTO vignette study were not used to inform the economic model, but provide validation of the values used in the economic model. Full details can be found in the TTO study report.[23]

B.3.4.4 Adverse reactions

As discussed in Section B.3.3.5, adverse events were not explicitly modelled within the economic analysis. However, some treatment-related disutilities capturing HRQoL impacts due to the inconvenience and burden related to current clinical management options were included within the model, described in Section B.3.4.5.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Baseline utility and age-adjustment

Baseline utility (i.e. when experiencing no modelled manifestations or treatments) was informed by the utility value generated for the APDS baseline health state in the clinician EQ-5D vignette study ([redacted]). The baseline utility was adjusted due to the HRQoL decrement with increasing age. For example, for the cycle during which the modelled population reached age 50 years, the baseline utility was multiplied by ratio of the general population utilities at age 50 versus 15 years.

Utility impact of manifestations and treatments

If a disutility or utility multiplier was not available, they were calculated as described below using utility values, assuming that the utility impact of a manifestation is independent of age.

The utility impacts of transient manifestations and short-term treatments were modelled by applying disutilities associated with the manifestation or treatment:

> Disutility per cycle = overall disutility * duration of the manifestation or treatment as a proportion of cycle length

Transient utility impacts of manifestations included the impact of infections (assumed to last 14 days for the purpose of calculating a disutility) and the impact of malignancy during the first year of occurrence. Transient utility impacts of treatments included the impacts of tonsillectomy, intravenous IRT (daily disutility associated with infusion) and HSCT (disutility within the first 100 days after HSCT).

The utility impacts of long-term manifestations (all other modelled manifestations) and continuous treatments (all other modelled treatments) were modelled by applying a utility multiplier:

> Utility multiplier = (utility with manifestation / age-adjusted UK general population utility)

Utility values in the economic analysis

Table 53 presents the utility values and utility impacts used in the base case economic analysis.

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Table 53. Utility data in the economic model

Input description	Utility, disutility or multiplier	SE	Weighting (%)	Source condition	Source	HRQoL methods	Rationale
Baseline							
APDS baseline utility (no modelled manifestations or treatments)	[redacted]	0.01	N/A	APDS	Clinician EQ-5D vignette study	• EQ-5D-5L completed by clinicians • Mapped to EQ-5D-3L index scores (Hernandez Alava 2020)[315]	• There are no literature-based estimates of the utility of asymptomatic APDS (or IEIs in general).
Manifestations							
Splenomegaly utility multiplier	0.91	0.09	N/A	Myelofibrosis	• Utility with splenomegaly (0.71) at mean age 65 years: Mesa et al., 2021[316] • General population utility at age 65 years (0.78): Kind et al., 1999[317] • 0.71 / 0.78 = 0.91	EQ-5D-3L (UK value set: Dolan et al., 1997)[318]	• It is assumed that the utility impact of splenomegaly is representative of the utility impact of persistent lymphoproliferation • Splenomegaly is a major clinical manifestation of myelofibrosis, and the symptoms of splenomegaly are relatively similar between APDS and myelofibrosis, therefore myelofibrosis was deemed an acceptable proxy condition
Gastrointestinal disorder utility multiplier	0.46	0.05	N/A	Inflammatory bowel disease (IBD)	• Utility with IBD (0.42) at age 35-40: Wilson and Lucas, 2018[319] • General population utility at age 35–40 years (0.91): Kind et al., 1999[317] • 0.42 / 0.91 = 0.46	Methods unclear (likely a disease-specific measure completed by patients, mapped to EQ-5D, and valued using UK value set by Dolan et al, 1997)[318]	• Proxy condition validated in Expert Consultancy project[14] • As validation of the utility value of 0.42 (given the unclear methods), Woehl et al., 2008 reported a utility value of 0.41 for ulcerative colitis using EQ-5D-3L (NICE TA856)[320]

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Cytopenia utility multiplier	0.88	0.09	N/A	Immune thrombocytopenic purpura (ITP)	• Cytopenia in ITP utility (0.75) at mean age 46: Snyder et al., 2008[321] • General population utility at age 46 years (0.85): Kind et al., 1999[317] • 0.75 / 0.85 = 0.88	• EQ-5D completed by patients • US value set: Shaw et al., 2005[322]	• Proxy condition validated in Expert Consultancy project[14] • Other identified studies did not use EQ-5D
Malignancy disutility (first year only)	-0.48	0.05	N/A	APDS	Clinician EQ-5D vignette study	• EQ-5D-5L completed by clinicians • Mapped to EQ-5D-3L index scores (Hernandez Alava 2023)[315] • The lymphoma utility multiplier from the clinician EQ-5D vignette study was 0.48 • Calculated as: (Lymphoma utility multiplier * baseline utility - baseline utility) - (DLBCL multiplier * baseline utility - baseline utility)	• The utility impact of DLBCL in the next row was estimated based on a population substantially older than the APDS population diagnosed with malignancies, and considers the patient's lifetime as a whole, therefore not capturing the impact experienced during the first year of developing a malignancy • Therefore, the EQ-5D exercise responses were used to inform the mean estimated additional disutility during the first year when a patient develops malignancy • This disutility was applied in addition to the DLBCL utility multiplier (next row) in the first year of malignancy onset; for the following cycle and beyond, the utility impact of malignancy reverted to that of the DLBCL utility multiplier alone

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Malignancy utility multiplier (first year and beyond)		0.86	0.09	N/A	Diffuse large B-cell lymphoma	• Utility with DLBCL (0.69) at age 61: Launonen et al., 2021 • General population utility at age 61 years (0.8): Kind et al., 1999[317] • 0.69 / 0.8 = 0.86	• EQ-5D-3L completed by patients • UK value set: Dolan et al., 1997[318]	• Proxy condition validated in Expert Consultancy project[14] • Diffuse large B-cell lymphoma was the most prevalent malignancy in individuals with APDS in the SLR by Jamee et al., 2019[18] • Utility data from Launonen et al., 2021 were used in NICE TA821[323, 324]
Infections	Moderate lower respiratory infections disutility	-0.003	0.01	26	Not disease-specific	• Proportion of patients: based on the proportion of observed infection events in the ESID registry (November 2023 dataset) qualifying as moderate lower respiratory events (chest infection: 98 events), severe lower respiratory infections (pneumonia: 80 events), moderate upper respiratory infections (otitis media: 89 events; sinusitis: 66 events), and herpes zoster (chronic viral infections: 46 events)[16] • Disability weights: Global Burden of Disease Study 2019, [325] recalculated based on a duration of 23.4 days per infection (estimated based on 123 infections observed in up to four years of follow-up in Study 2201E1, with a total of 2,879 days of infection in the same period)[38]	Disability weights based on a global survey (including European countries) that used pairwise comparison methods in which respondents were asked to indicate which of two health states briefly described to them they considered to be "healthier"[325]	Disability weight estimated from data across multiple diseases
	Severe lower respiratory infections disutility	-0.009	0.01	21				
	Moderate upper respiratory infections disutility	-0.003	0.01	41				
	Herpes zoster disutility	-0.004	0.01	12				
	Infections: weighted average disutility	-0.004	N/A	100				

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Bronchiectasis utility multiplier		0.91	0.09	N/A	Bronchiectasis	• Utility with bronchiectasis (0.7) at age 66: Brockwell et al., 2020[326] • General population utility at age 66 years (0.8): Kind et al., 1999[317] • 0.7 / 0.8 = 0.91	• EQ-5D-3L completed by patients • UK value set: Dolan et al., 1997[318]	N/A
Advanced lung disease utility multiplier		0.65	0.06	N/A	Cystic fibrosis	• Utility with cystic fibrosis (0.6) at age 28.5: Bradley et al., 2013[327] • General population utility at age 28.5 years (0.93): Kind et al., 1999[317] • 0.6 / 0.93 = 0.64	• EQ-5D completed by patients • UK value set: MVH group[328]	Proxy condition validated in Expert Consultancy project[14]
Hearing loss	Mild hearing loss disutility	-0.01	0.001	50	Not disease-specific	• Disability weights: Global Burden of Disease Study 2019[325] • Proportion of patients: assumption	Disability weights	Disability weight estimated from data across multiple diseases. This is likely to be an underestimate of the utility impact of hearing loss due to the difficulty of measuring HRQoL with this condition
	Moderate hearing loss disutility	-0.027	0.003	50				
	Weighted average	-0.02	N/A	N/A				
Treatments								
IRT	SCIG disutility	0.000	0.000	64.8	N/A	• IVIG disutility: Weeks, Tierney and Weinstein, 1991 report an annual disutility of 0.0075 assuming infusions every 4 weeks;[329] the disutility was recalculated assuming infusions every 3 weeks: 0.0075 * 4/3 = 0.01 • SCIG disutility: assumption • Proportions of patients: assumption	N/A	Conservative assumption
	IVIG disutility	-0.010	0.001	35.2	Chronic lymphocytic leukaemia		Reference gamble approach with clinicians	N/A
	Weighted average	-0.004	N/A	N/A	N/A		N/A	N/A

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HSCT disutility within the first 100 days	-0.57	0.06	N/A	Advanced follicular lymphoma	Sung et al., 2003[330]	Clinical expert opinion	• The risk of transplant-related complications and infections is the highest during the first 100 days post-transplantation • Aligned to HST18[331]
Tonsillectomy disutility	-0.05	0.01	N/A	Paediatric obstructive sleep apnoea	Disutility associated with complications (mainly haemorrhage) Bagwell et al., 2018[332]	NR	N/A

Abbreviations: APDS: Activated PI3K Delta Syndrome; DLBCL: Diffuse Large B-Cell Lymphoma; ESID: European Society for Immunodeficiencies; HRQoL: Health-Related Quality of Life; HSCT: Hematopoietic Stem Cell Transplantation; IBD: Inflammatory Bowel Disease; ITP: Immune Thrombocytopenic Purpura; IVIG: Intravenous Immunoglobulin; MVH: Measurement and Valuation of Health; N/A: Not Applicable; NICE TA: National Institute for Health and Care Excellence Technology Appraisal; SCIG: Subcutaneous Immunoglobulin; SE: Standard Error; SLR: Systematic Literature Review; UK: United Kingdom.

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Approach to combining utility impacts

Starting from the baseline utility, an additive approach was assumed in order to combine the utility impacts of manifestations and treatments when more than one manifestation/treatment is experienced.

Utility impact of leniolisib

In case reports and patient narratives, it was stated that some manifestations improve, but do not fully resolve, with leniolisib treatment. Additionally, in the Expert Consultancy (Exercise 4, Quantitative), clinicians were asked "What proportional improvement in days unable to work or participate in education would you estimate if the clinical manifestations of the disease were improved by 50%?", to which their average answer was 72%. Therefore, it was assumed in the economic model that for patients experiencing improvement in severity of manifestations due to leniolisib treatment (see B.3.3.4), the utility decrement due to those manifestations would be concurrently reduced by 50%.

Additionally, as described in Section B.1.4.2, living with APDS has broad and substantial emotional impacts on individuals with APDS, including anxiety, depression, stress, fatigue and "having no hope for the future".[11, 23, 108, 109] Participants treated with leniolisib in Study 2201 reported improvements in aspects of APDS that were not modelled, such as increased energy during the study periods, or improvements in manifestations not captured within the model.[17, 27, 35, 38] People receiving leniolisib are also expected to benefit from a reduced emotional burden of APDS due to the lower expected risk of developing lymphoma and mortality, and increased hope due to the availability of a new treatment.[11, 23, 284] Some studies have quantified the impacts of a positive view, optimism and anxiety using EQ-5D, and the magnitude of these impacts were similar with an approximate utility gain of 0.1. To incorporate the long-term QoL impact of leniolisib treatment on the overall wellbeing of patients, associated with increased vitality and reduced anxiety over and above the direct impact of the reduction in modelled manifestations, a utility gain of 0.1 was applied for those in the "Alive and on leniolisib treatment" health state.

Additionally, while quantifiable data on the caregiver impact of leniolisib is lacking, anecdotal evidence highlights positive improvements in caregivers' lives following leniolisib treatment, further supporting the broader benefits of leniolisib beyond the benefit to the patient captured in the economic model. However, these gains are relevant to a societal perspective and have not been included in the model.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The economic analysis takes an NHS and PSS perspective in line with the NICE reference case. Appropriate sources of unit costs, such as NHS reference costs 2020/21, the British National Formulary (BNF) costs, the electronic Marketing Information Tool (eMIT) and other published sources were used to inform the cost inputs in the model. Where required, the costs were inflated to 2022 GBP using the NHS cost inflation index.

As discussed in Section B.3.1 and Appendix I, the costs/HCRU SLR identified three studies that specifically reported on costs and HCRU in APDS. However, none provided useful evidence relevant to the decision problem for this evaluation. As discussed in Appendix I, the study by Harrington et al., 2023 was performed from a US perspective and did not report the

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characteristics of the patient population or report upon specific treatments;[117] Ariue et al., 2020 does not report HCRU data relevant to this economic model.[333]

In the absence of published sources of evidence, cost/resource inputs included in the model were based on results from the quantitative survey of the Expert Consultancy project (Exercise 4).[14]

B.3.5.1 Intervention and comparators' costs and resource use

Leniolisib costs

Drug acquisition costs for leniolisib were calculated by dosage. As individuals with APDS are administered leniolisib 70 mg bid and the cost per bottle of 60 tablets is £[redacted] (list price, excluding VAT). When including the proposed PAS for leniolisib, the annual cost of leniolisib per patient is be £[redacted]; see Table 71 in Appendix K for further details. As an oral therapy, no administration costs were included for leniolisib. Full treatment compliance was assumed, based on the >99% compliance rate observed over a median of 154.71 weeks in Study 2201E1.

Current clinical management costs

Costs associated with current clinical management in the economic model are summarised in Table 54; wastage was assumed for all treatments.

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Table 54: Summary of current clinical management costs in the economic model

Treatment/ manifestation	Cost	Unit	Summary of cost	Summary of sources	Table in Appendix
Acute antimicrobials (acute infections)	£15.83	Per infection episode	Weighted average drug cost of commonly used antibiotics, antifungals and antivirals for single infections	eMIT, SmPCs and other sources	Table 74 in Appendix K
Antimicrobial prophylaxis (history of infection)	£205.47	Per year	Weighted average drug cost of commonly used antibiotics, antifungals and antivirals for prophylaxis	eMIT, SmPCs and other sources	Table 74 in Appendix K
IRT	Current clinical management: £44,220.49 Leniolisib: £[redacted] to £43,502.44	Per year	Weighted average of SCIG and IVIG costs, costs for leniolisib based on reductions in dose and proportions of patients receiving IRT with leniolisib	BNF, Study 2201 Part II	Table 81 in Appendix K
Immunosuppressive treatments	£2,265.97	Per year	Weighted average of sirolimus, rituximab, mycophenolate mofetil and cyclosporin (applies only to current clinical management arm)	BNF, SmPCs, EMA, Study 2201 Part II and other sources	Table 79 in Appendix K
Steroids	£0.90	Per year	Cost of prednisone (28 x 5 mg tablets)	BNF, eMIT	Table 80 in Appendix K
Tonsillectomy	£2,501.18	Per tonsillectomy	Cost of tonsillectomy	NHS reference costs 2021/22	Table 83 in Appendix K
HSCT (first 2 years)	£183,243.99	Per HSCT	Cost of bone marrow harvest, bone marrow transplant, allogeneic graft and follow up	NHS reference costs 2021/22	Table 82 in Appendix K

Abbreviations: AAD: antibiotic-associated diarrhea; AAP: American Academy of Pediatrics; ACS: acute coronary syndrome; ADHD: attention-deficit/hyperactivity disorder; AHA: American Heart Association; AIDS: acquired immunodeficiency syndrome; AML: acute myeloid leukemia; ANA: antinuclear antibody; ARDS: acute respiratory distress syndrome; ASD: autism spectrum disorder; BBB: blood-brain barrier; BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CBC: complete blood count; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CSF: cerebrospinal fluid; CT: computed tomography; CVA: cerebrovascular accident; DVT: deep vein thrombosis; ECG: electrocardiogram; EEG: electroencephalogram; ENT: ear, nose, and throat; ESR: erythrocyte sedimentation rate; GERD: gastroesophageal reflux disease; HIV: human immunodeficiency virus; ICU: intensive care unit; IUD: intrauterine device; LFT: liver function test; MRI: magnetic resonance imaging; MS: multiple sclerosis; NPO: nil per os (nothing by mouth); NSAID: non-steroidal anti-inflammatory drug; OCD: obsessive-compulsive disorder; PCP: primary care physician; PET: positron emission tomography; PTSD: post-traumatic stress disorder; RBC: red blood cell; SARS: severe acute respiratory syndrome; SLE: systemic lupus erythematosus; STI: sexually transmitted infection; TB: tuberculosis; TIA: transient ischemic attack; UTI: urinary tract infection; VTE: venous thromboembolism; WBC: white blood cell.

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B.3.5.2 Health-state unit costs and resource use

Manifestation costs

Costs associated with manifestations are summarised in Table 55.

During the Expert Consultancy (Exercise 4), the average estimated reduction across clinicians in the use of antibiotics (acute and prophylactic), immunosuppressives, mTOR inhibitors, IRT and surgical procedures when leniolisib becomes available was 65%.[14] Therefore, for individuals in the "Alive on leniolisib treatment" state experiencing a reduction in the severity of gastrointestinal manifestations, cytopenia, bronchiectasis and/or advanced lung disease (Section B.3.3.4), a 50% reduction in the costs associated with the manifestations with reduced severity was assumed (see tables in Appendix K for costs weighted according to the proportions of patients modelled to experience the reduction in severity with leniolisib).

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Table 55: Summary of manifestation costs in the economic model

Manifestation	Cost per cycle for patients experiencing manifestation	Summary of cost	Summary of sources	Table in Appendix
Lymphoproliferation	No associated cost of lymphoproliferation (assumption)			
Infections	See Table 54 (antimicrobials)			
Cytopenia	£7,377.42	Frequency-weighted cost of transfusion, biopsy and corticosteroid treatment	TA853, NHS reference costs 2021/22, BNF and Expert Consultancy (Exercise 4)	Table 73 in Appendix K
Gastrointestinal manifestations	£2,348.68	Frequency-weighted cost of procedures and medication	NHS reference costs 2021/22, BNF, TA856, Expert Consultancy (Exercise 4) and other sources	Table 72 in Appendix K
Malignancy (lymphoma)	£29,839.12	Frequency-weighted cost of procedures, treatment and care	NHS reference costs 2021/22, BNF, Expert Consultancy (Exercise 4) and other sources	Table 75 in Appendix K
Bronchiectasis-associated airway disease	£20,329.12	Frequency-weighted cost of tests, procedures, treatment, ventilation and care	NHS reference costs 2021/22, BNF and Expert Consultancy (Exercise 4)	Table 76 in Appendix K
Advanced lung disease	£30,679.06	Frequency-weighted cost of tests, procedures, treatment, ventilation and care	NHS reference costs 2021/22, BNF and Expert Consultancy (Exercise 4)	Table 77 in Appendix K
Hearing loss	£1,273.39	Weighted average cost of mild and moderate hearing loss due to chronic otitis media	NHS reference costs 2020/21	Table 78 in Appendix K

Abbreviations: BNF: British National Formulary; CM: current clinical management; NHS: National Health Service; SmPC: Summary of Product Characteristics; TA: technology appraisal.

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Monitoring costs

As discussed in Section B.1.4.3, people with APDS are often treated by a multidisciplinary clinical care team based on their presenting manifestations.[14] The economic model included monitoring costs for visits to various specialists. With long-term leniolisib treatment, it is expected that monitoring costs would decrease compared with individuals receiving current clinical management, in line with disease stabilisation.

As part of the Expert Consultancy project (Exercise 4, quantitative), clinicians estimated the following quantities for patients receiving leniolisib and patients receiving current clinical management:[14]

- The numbers of visits to each specialist per year
- The proportions of patients who would visit each specialist (for leniolisib, clinicians provided estimates assuming disease stabilisation)

The results of this exercise were used to calculate monitoring costs for leniolisib and current clinical management in the economic model (Table 56).

For the cohort of individuals discontinuing leniolisib treatment (i.e. entering the “Alive not on leniolisib treatment” state), monitoring costs reverted back to those under current clinical management.

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Table 56. Monitoring costs for visits to various specialists

Description	Cost per visit (£)	Reference	Remarks	Leniolisib		Current clinical management	
				Number of visits per year	Proportion of patients attending each visit	Number of visits per year	Proportion of patients attending each visit
Immunology-physician visit	335.47	NHS reference costs FY21-22	CL, WF01A, Clinical Immunology, Non-Admitted Face-to-Face Attendance, Follow-up	1.69	0.76	3.20	0.98
Immunology-nurse visit	24.00	PSSRU 2022	Assume half an hour visit length, cost per hour (£48) for band 5 hospital based nurse including qualification	0.73	0.76	2.80	0.88
GP	41.00	PSSRU 2022	For average GP consultation (9.22 minutes), with qualification costs, including direct care staff cost	3.50	0.82	7.00	0.98
Respiratory Medicine visit	194.30	NHS reference costs FY21-22	CL, WF01A, Respiratory Medicine, Non-Admitted Face-to-Face Attendance, Follow-up	1.00	0.51	2.13	0.83
Gastroenterologist visit	182.93		CL, WF01A, Gastroenterology, Non-Admitted Face-to-Face Attendance, Follow-up	0.75	0.11	2.30	0.42
Haematology visit	209.41		CL, WF01A, Clinical Haematology, Non-Admitted Face-to-Face Attendance, Follow-up	0.33	0.09	2.20	0.37
Haematologist - bone marrow transplant (BMT) specific	416.39		CL, WF01A,Blood and Marrow Transplantation Service, Non-Admitted Face-to-Face Attendance, Follow-up	4.50	0.34	6.90	0.34
Genetic counselling	473.14		CL, WF01A,Clinical Genetics Service, Non-Admitted Face-to-Face Attendance, Follow-up	1.00	0.56	1.50	0.74
Outpatient infusion centre	295.05		AB18Z, Continuous Infusion of Therapeutic Substance for Pain Management, service code: 191	10.00	0.24	12.40	0.60

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Physiotherapist	82.52		CL, WF01A,Physiotherapy Service, Non-Admitted Face-to-Face Attendance, Follow-up	0.33	0.15	1.88	0.45
Psychologist	351.12		CL, WF01A,Clinical Psychology Service, Non-Admitted Face-to-Face Attendance, Follow-up	3.00	0.16	9.00	0.45
Total cost per cycle (annual)				**2,457.88**		**7,271.18**	

Abbreviations: BMT: bone marrow transplant; CL: code list; FY: fiscal year; GP: general practitioner; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; WF01A: weighted face-to-face outpatient attendance.

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B.3.5.3 Adverse reaction unit costs and resource use

As discussed in Section B.3.3.5, adverse events were not modelled within the economic analysis.

B.3.5.4 Miscellaneous unit costs and resource use

No other costs were included beyond those defined above.

B.3.6 Uncertainty

Structural uncertainty

Considering that APDS is an ultra-rare, progressive, recently described condition, research in this indication is evolving;[1, 2, 13] therefore, there is a possibility that with advancing research, additional aspects of APDS and benefits of leniolisib may not have been captured in the model. However, the model has undergone validation to ensure it does comprehensively and accurately represent the known impact of APDS on HRQoL and the healthcare system, and the impact of leniolisib (see Section B.3.13 for more detail).

For people with APDS, PI3Kδ levels have short- and long-term impact on immune function and associated symptoms. The model included manifestations and treatments with known associations with APDS, established in the literature and confirmed with expert judgement. These manifestations and treatments were also confirmed by clinical trial data, real-world evidence on the use of leniolisib and modified SEE[14] to be impacted by leniolisib, hence their inclusion in the model. Finally, surrogate endpoint exploration revealed associations between 12-week clinical trial results and long-term improvements HRQoL and reducing infections.[270] There is confidence that the results of the clinical evidence sources indicate long-term improvements to manifestations and treatments utilisation, and hence confidence in the ability of the model structure to accurately capture the benefits of leniolisib treatment.

In the absence of accepted definitions of response or rates of disease regression in APDS,[162] the model instead tracked the age-specific incidence and prevalence of manifestations and treatment use. Therefore, the utility impacts of individual manifestations (and treatments) had to be combined in the mode, for which an additive approach was used. The base case utility impacts were combined using the additive method to estimate the utility values associated with the combinations of manifestations defined in the 12 vignettes used in the clinician EQ-5D vignette study.[311] The resultant combined impacts were compared against the clinician EQ-5D vignette study utility values (Table 57). Combining base case utility impacts using the additive method results in greater utility impacts compared with clinician EQ-5D vignette study results.[311] In line with this, a recent study by Thompson et al., 2019[334] found that the additive method generally performed well, but tends to underestimate utility for severe health states.

Table 57: Estimated utility values for combinations of manifestations from EQ-5D exercise, and using additive approach based on proxy conditions

Vignette	Utility value from clinician EQ-5D vignette study	Combined utility values from proxy conditions
APDS general (baseline health state)	[redacted]	N/A

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APDS general + infections + lymphoproliferation	[redacted]	[redacted]
APDS general + infections + lymphoproliferation + bronchiectasis	[redacted]	[redacted]
APDS general + infections + lymphoproliferation + cytopenia	[redacted]	[redacted]
APDS general + infections + lymphoproliferation + GI	[redacted]	[redacted]
APDS general + infections + lymphoproliferation + bronchiectasis + cytopenia + GI	[redacted]	[redacted]
APDS general + infections + lymphoproliferation + lymphoma	[redacted]	[redacted]
APDS general + infections + lymphoproliferation + bronchiectasis + cytopenia + GI + lymphoma + fatigue + hearing loss	[redacted]	[redacted]

Abbreviations: GI: gastrointestinal manifestations.

Parameter sources

In order to inform manifestation and treatment use rates, survival and the utility impacts of manifestations and treatments, various sources were available. The choice of sources for the base case are described in Sections B.3.3.2, B.3.3.3 and B.3.4.5, respectively, based on what Pharming believe to be the most appropriate and robust data to inform the economic model. To explore uncertainty in the choice of parameter sources, scenario analyses included different sources of evidence (Section B.3.10.3).

Parameter precision

As discussed in Section B.1.4.1 and throughout this submission, APDS is an ultra-rare condition that has only recently been described;[2] therefore, data sources are scarce and if available, usually limited to smaller sample sizes, which in turn may give rise to uncertainty around mean parameter values (i.e. precision).

In order to understand the uncertainty associated with the ESID data used in the model, a modified SEE was conducted as part of the Expert Consultancy with clinicians (Exercise 1). Clinicians' lower and upper estimates for manifestation rates in the modified SEE allowed validation of the manifestation rates for individuals with APDS provided by the ESID registry, minimising the associated parameter uncertainty in the model.[14]

The impact of leniolisib on manifestations in the economic model was informed by a collective body of evidence, including responder analyses of data from Study 2201E1 based on thresholds derived via a Delphi panel of clinical experts, data from real-world use of leniolisib in the EAP, and expert insights collected through robust methods as part of the Expert Consultancy.[39, 64, 266, 276] Data from the responder analyses and EAP survey were assumed to apply in the long term in the economic model.[39, 64, 276] Although the evidence generated by expert elicitation is subject to risk of bias and uncertainty, structured approaches were utilised and the modified SEE methodology employed was designed under consideration of the York Centre for Health Economics reference protocol for expert elicitation in HTA.[67]

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Finally, with regards to proxy utility values, full details of the methodology that had been used to generate these utility data were not always available, and non-reference case methods were used to generate utility values, creating uncertainty in the precision of the utility estimates. However, as described in Section B.3.4.5, utility estimates were chosen based on a number of factors including generalisability to the UK APDS population and consideration of the NICE reference case.[335]

Therefore, we ask the Committee to consider that approaches to generating evidence have been tailored to overcome the challenges and limitations inherent to an ultra-rare condition, first described in 2013, with an evolving evidence base, and that uncertainty has been mitigated where possible.

B.3.7 Managed access proposal

Pharming does not wish to present a managed access proposal for leniolisib at this stage.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of the numerical inputs described above that are used for the base case is presented in Table 58.

Table 58: Summary of variables applied in the economic model

Variable	Value (or reference to table or figure in submission)	Reference to section in submission
Clinical parameters		
Baseline age	15 years	B.3.3.2
Manifestation rates under current clinical management	Figure	B.3.3.2
Treatment use rates under current clinical management	Figure	B.3.3.2
Overall survival under current clinical management	Figure	B.3.3.3
Impact of leniolisib on manifestations	Table to Table	B.3.3.4
Impact of leniolisib on treatment use	Table	B.3.3.4
Impact of leniolisib on overall survival	Figure	B.3.3.4
Annual discontinuation rate	3.54%	B.3.3.6
Utility inputs		
Baseline utility value	[redacted]	B.3.4.5
Utility impacts of manifestations and treatments	Table	B.3.4.5
Utility improvement for less severe state	50%	B.3.4.5
Utility impact of leniolisib treatment	+0.1	B.3.4.5

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Cost and resource use inputs		
Cost of leniolisib per patient per year (with proposed PAS)	£[redacted]	B.3.5.1
Current clinical management treatment costs	Table	B.3.5.1
Manifestation costs	Table	B.3.5.2
Resource use reduction for less severe disease state	50%	B.3.5.2
Monitoring costs	Table	B.3.5.4
Settings		
Time horizon	Lifetime	B.3.2.2
Discount rate for costs	3.5%	B.3.2.2
Discount rate for health effects	1.5%	B.3.2.2

Abbreviations: PAS: patient access scheme.

B.3.8.2 Assumptions

An overview of the key modelling assumptions taken in the base case is provided in Table 61.

Table 59: Summary of assumptions used in the economic model

Assumption	Reference in submission	Justification/validation
Efficacy and safety from the leniolisib clinical trials, EAP survey and Expert Consultancy (Exercise 1) can be generalised to the UK clinical setting	B.3.3	• In the Expert Consultancy (Exercise 3), the clinical experts were asked to validate the generalisability of the Study 2201 Part II study population to the UK clinical APDS population. All participants agreed that the baseline demographics and disease characteristics were generalisable to their respective region's population of people with APDS[14] • Given that the majority of individuals in the EAP were from Europe and the Russian Federation at the time of the survey, including 6 individuals from the UK, it is expected that the findings from the EAP are generablisable to clinical practice in the UK[43] • Exercise 1 of the Expert Consultancy included clinicians from the UK (n=2), as well as Italy, Spain and Canada, where clinical practice and patient demographics are expected to be relatively similar to the UK[14]
Data from the responder analyses and EAP survey were assumed to apply in the long-term in the economic model	B.3.3.4	There is no evidence of treatment waning across the evidence base for leniolisib, including with up to six years of follow-up in Study 2201E1[38]
It was assumed that for a cohort of patients discontinuing leniolisib treatment, the cumulative	B.3.3.6	Changes to the constitution of the immune system may occur over a period of several years.[280, 281] Assuming a jump in

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proportions of patients experiencing manifestations or using treatments would increase at a constant rate to the levels in the current clinical management arm, with the constant rate equal to the average incidence of manifestations under current clinical management		manifestation rates post-discontinuation of leniolisib to the rates under current clinical management would require the cohort to experience a higher incidence of manifestations or treatment use in the "catch-up" period than those in the current clinical management arm
Adverse events were not included in the model	B.3.3.5	Adverse events were assumed to have a similar impact on HRQoL and costs between the leniolisib and current clinical management arms of the model
Where multiple subtypes of manifestations could inform a proxy utility (e.g. lymphoma, autoimmunity) a representative manifestation subtype was chosen based on prevalence	B.3.3	Choice based on clinical expert opinion
Manifestations experienced in the proxy conditions can be considered similar to APDS manifestations in terms of utility impact	B.3.4.3	In most cases, validated during the Expert Consultancy[14]
Additive approach to combining utilities	B.3.4.5	There is no accepted method to combine utility impacts; an additive approach was considered appropriate in this scenario
It was assumed that people receiving leniolisib would need to discontinue leniolisib treatment before receiving HSCT	B.3.3.6	Based on experience in the EAP to date[263]
A 50% reduction in the utility impact and costs associated with manifestations was assumed for individuals experiencing a reduction in severity of these manifestations	B.3.3.4	The 50% reduction in the utility impact is based on case reports and patient narratives, in which it is stated that some manifestations improve but do not fully resolve. Additionally, in the Expert Consultancy (Exercise 4), clinicians estimated that there would be a 72% proportional improvement in days unable to work or participate in education if the clinical manifestations of the disease were improved by 50%[14] As part of the Expert Consultancy (Exercise 4), clinicians estimated an average reduction of 65% in the use of current clinical management treatments for people on leniolisib treatment[14] A reduction of 50% was therefore chosen as a valid assumption for both utility impacts and costs
It was assumed that people on leniolisib treatment would experience a utility gain of 0.1	B.3.4.5	Participants treated with leniolisib in Study 2201 reported improvements in aspects of APDS that were not modelled, such as increased energy during the study periods, or improvements in manifestations not captured

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		within the model.[17, 27, 35, 38] People receiving leniolisib are also expected to benefit from a reduced emotional burden of APDS due to the lower expected risk of developing lymphoma and mortality, and increased hope due to the availability of a new treatment. Moreover, the model does not include various manifestations that leniolisib treatment has been shown to benefit, thereby underestimating its potential benefit. Additionally, while quantifiable data on caregiver impact is lacking, anecdotal evidence highlights positive improvements in caregivers' lives, further supporting the broader benefits of leniolisib beyond what the model captures. Based on previous studies, a utility gain of 0.1 is expected to capture the overall improvement in the wellbeing of patients associated treated with leniolisib.

Abbreviations: APDS: Activated PI3K Delta Syndrome; EAP: Early Access Program; HRQoL: Health-Related Quality of Life; HSCT: Haematopoietic Stem Cell Transplant.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The deterministic and probabilistic base case analysis results are presented in Table 60 and Table 61, respectively, expressed in terms of costs, QALYs, ICER and net health benefit (NHB). For all results, leniolisib has been included at proposed PAS price and the comparator at list prices.

In the base case deterministic analysis, leniolisib was associated with increased health benefits compared with current clinical management of 14.8 undiscounted QALYs, in alignment with the clinical and HRQoL improvements observed with leniolisib in the clinical trials. Therefore, a weighting of 1.5 was applied to the discounted QALYs for leniolisib. In the deterministic and probabilistic analyses, leniolisib was associated with a gain of 15.46 discounted, weighted QALYs and 17.10 discounted, weighted QALYs, respectively, compared with current clinical management. Leniolisib was also associated with higher costs than current clinical management. However, overall, leniolisib was found to be plausibly cost-effective compared with current clinical management at a willingness-to-pay threshold of £100,000/QALY, yielding ICERs of £[redacted]/QALY (deterministic) and £[redacted]/QALY (probabilistic).

Deterministic and probabilistic results without QALY weighting of 1.5 are also provided in Table 60 and Table 61, respectively. Disaggregated results from the base case cost-effectiveness analysis are presented in Appendix J.

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Table 60: Deterministic base-case results, with QALY weighting (with proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Weighted incremental QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.46	15.46	[redacted]	[redacted]
Current clinical management	1,587,334	34.81	[redacted]	-	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 61: Probabilistic base-case results, with QALY weighting (with proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Weighted incremental QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.57	17.10	[redacted]	[redacted]
Current clinical management	1,613,679	34.77	[redacted]	-	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

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B.3.10 Exploring uncertainty

As detailed in Section B.3.6, model parameters were associated with uncertainty as would be expected in an ultra-rare disease which was first described relatively recently.[1, 2] In order to assess the impact of parameter uncertainty on the economic model results, both probabilistic and deterministic sensitivity analysis were conducted, the results of which are presented in Sections B.3.10.1 and B.3.10.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.10.3.

Overall, it is considered that relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined effect of uncertainty from parameter precision on the results of the cost-effectiveness analysis. Probability distributions were assigned to each parameter (aside from survival parameter), to characterise uncertainty associated with the precision of the mean values, based on the nature of each parameter. Where empirical probability distributions were not available, the standard error was assumed to take a value equal to 10% of that of the mean. Full details of the inputs used in the PSA are presented in Appendix P. The PSA was run for 1,000 iterations, in each of which model inputs were randomly sampled from the specified probability distributions.

The cost-effectiveness plane and acceptability curves are presented in Figure 25 and Figure 26, 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, with QALY weighting, or a [redacted]% probability of being cost-effective at a £100,000/QALY threshold without QALY weighting. The PSA results were aligned with the deterministic base case results, indicating that the base case ICER is robust to uncertainty in parameter precision.

As shown in the stability plot presented in Figure 27, the net monetary benefit (NMB) associated with leniolisib versus current clinical management changes <1% per iteration after 87 iterations, and <0.1% after 978 iterations. As such, 1,000 iterations was considered a suitably high number for the PSA to assess the uncertainty of simultaneously varying inputs in the model.

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Figure 25: Scatterplot of probabilistic results

Figure 26: Cost-effectiveness acceptability curve

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Figure 27: NMB stability plot

Abbreviations: NMB: net monetary benefit.

B.3.10.2 Deterministic sensitivity analysis

In order to further assess the robustness of the base case model results and identify drivers of the ICER, deterministic sensitivity analysis (DSA) was conducted by varying each model input individually. Where empirical 95% CIs were not available, a SE of 10% of the mean was assumed. Parameters were varied within lower and upper bounds set to 2.5% and 97.5% of their 95% CIs.

The results of the DSA are presented in Figure 28. The parameters with the greatest influence on the ICER were the rate of gastrointestinal manifestations, the rate of advanced lung disease, and the long-term utility impact of lymphoproliferation and splenomegaly for standard care.

Figure 28: Results of the DSA

Abbreviations: DSA: deterministic sensitivity analysis, HR: hazard ratio, ICER: incremental cost-effectiveness ratio, IGRT: immunoglobulin replacement therapy (IRT), SoC: standard of care (current clinical management).

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B.3.10.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model results to alternative model inputs and assumptions. The probabilistic and deterministic base case results were similar (Section B.3.9.1), indicating that the economic model is linear; therefore, all scenario analyses were run deterministically.

Scenario #1: Manifestation-specific mortality

In the base case of the economic model, overall survival is informed by a case series of people with APDS identified by an SLR (described in Section B.3.3.3). However, different manifestations are associated with different mortality risks. For example, lymphoma is the dominant cause of mortality, resulting in 24–42% of all fatalities seen in APDS.[10, 13, 18, 107] Therefore, an alternative method for capturing the impact of leniolisib on mortality is through the expected reduction in manifestation rates with leniolisib, and the subsequent reduction in the risk of mortality due to each manifestation.

In this scenario analysis, the mortality risk associated with APDS manifestations was modelled. In the absence of data on the mortality risks associated with APDS manifestations in an APDS population, the mortality risks associated with each manifestation were obtained from a study by Odnoletkova et al., 2018 including people with CVID with non-infectious complications,[336] which was identified during the proxy disease-focused literature search. CVID with non-infectious complications has been identified as a candidate proxy disease for APDS.[312] The study reported the HRs of mortality for CVID comorbidities based on individuals in the ESID registry (Table 62). HRs for mortality due to infections and hearing loss were not reported by this study, despite severe respiratory infections being identified as a non-malignant cause of early mortality in APDS.[3, 12, 13, 18, 107] A conservative approach was therefore taken, assuming no impact on survival for these manifestations (i.e., HR=1). Additionally, in the short term, HSCT may also increase mortality (Section B.1.4.3). However, as a conservative assumption, no mortality risk associated with HSCT was modelled.

Table 62: HRs of mortality for each manifestation (scenario analysis #1)

Manifestations	HR[a]	Source
Lymphoproliferation	1.67	Odnoletkova et al., 2018[336]
Gastrointestinal manifestations	0.97	
Lymphoma	5.48	
Cytopenia	1.08	
Bronchiectasis	0.83	
Advanced lung disease[b]	4.85	
Infections	1	Assumption
Hearing loss	1	Assumption

Footnotes: [a]HRs represent a comparison of mortality risks with and without the manifestation within the CVID cohort e.g., mortality risk for CVID patients with lymphoma compared to CVID patients without lymphoma.
[b]Reported for granulomatous lymphocytic interstitial lung disease (GLILD).
Abbreviations: HR: hazard ratio.

The HRs from Odnoletkova et al., 2018 provided evidence on the impact of individual manifestations relative to each other on mortality, whereas people with APDS may experience multiple manifestations in combination, and additional manifestations to those investigated by

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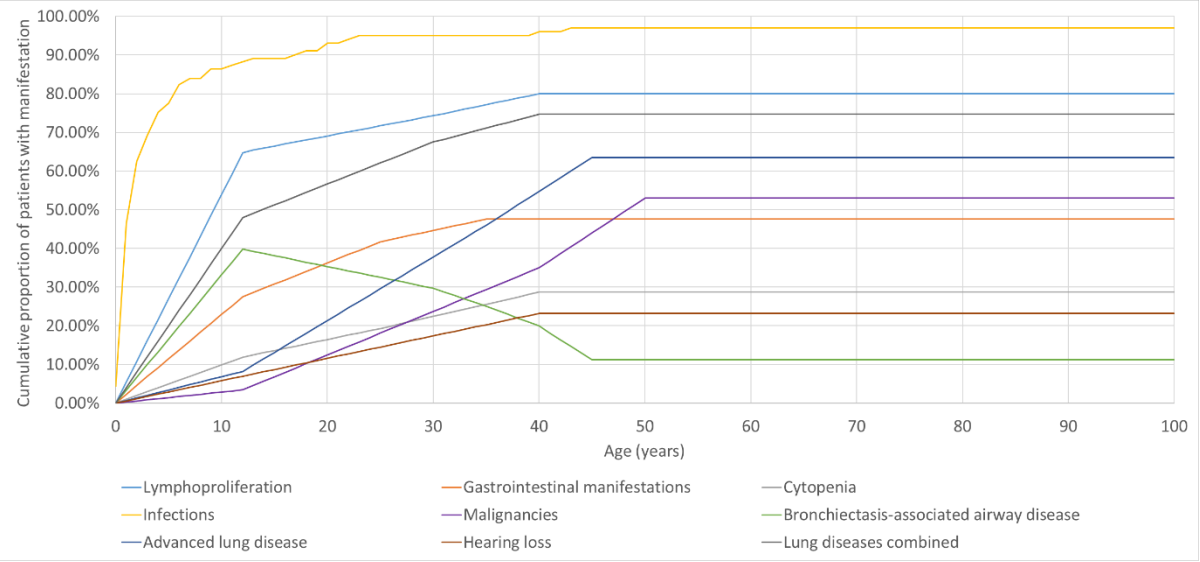
Odnoletkova et al.[336] Therefore, this method was likely to have underestimated the impact of APDS on survival (and hence the benefit of leniolisib), and a calibration factor was implemented in the model to ensure that predicted mortality in the current clinical management arm aligned with the observed mortality in people with APDS, as supported by HTA experts; this calibration factor was [redacted].

As shown in Table 66, changing the approach to modelling mortality slightly increased the ICER for leniolisib.

Scenario #2: Source of manifestation rates under current clinical management: modified SEE clinician estimate

Within the base case model, age specific manifestation rates under current clinical management are informed by the cohort of individuals with APDS in the ESID registry, and by data from Study 2201 Part II, as described in Section B.3.3.2.[66, 302] To assess the robustness of the cost-effectiveness results to the source of manifestation rates, in this scenario, manifestation rates under current clinical management were informed by the midpoint estimates of manifestation rates at each age from Exercise 1, Part 1 of the modified SEE (Expert Consultancy project). Please see Table 41 for further details.[14] Cumulative incidence plots displaying the manifestation rates used within this scenario are presented in Figure 29. The numerical data informing this scenario (incidence and cumulative incidence) are available within the economic model.

Figure 29: Manifestation rates for scenario #2, informed by modified SEE estimates



Footnotes: Advanced lung disease is a subset of bronchiectasis-associated airways disease; therefore, to prevent double counting of costs and utility impacts in the economic model, the cumulative proportion of individuals with advanced lung disease was calculated by subtracting the proportion with bronchiectasis-associated airway disease from the total proportion with 'lung disease combined'. This allowed manifestations to be mutually exclusive in the economic model. Therefore, the proportion with bronchiectasis-associated airway disease decreases with increasing age, as patients progress to develop advanced lung disease. 'Lung disease combined' is shown for information only, and does not represent a manifestation included in the model.
Abbreviations: APDS: activated PI3K delta syndrome, ESID: European Society for Immunodeficiencies.

As shown in Table 66, changing the source data to the clinician estimate slightly increased the ICER for leniolisib versus current clinical management.

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Scenario #3: Impact of leniolisib on manifestations: modified SEE clinician estimate

Within the base case analysis, HRs for the impact of leniolisib on the incidence, severity and resolution of manifestations were based on a variety of evidence sources, including: the leniolisib clinical trial programme (Study 2201 Part II and 2201E1), the leniolisib EAP, and a modified SEE (Exercise 1 of the Expert Consultancy) [see Section B.3.3.4]. In this scenario, HRs for the impact of leniolisib on the incidence and resolution of manifestations, calculated from the modified SEE (Exercise 1 of the Expert Consultancy), were used (Table 41).[14] The modelling of infections remained unchanged from the base case.

Table 63: HRs for incidence and severity reductions of manifestations from the modified SEE (scenario analysis #3)

Manifestation	HR for incidence	HR for resolution
Lymphoproliferation	0.31	0.71
Cytopenia	0.65	0.51
Gastrointestinal manifestations	0.69	0.57
Bronchiectasis-associated airway disease	0.58	0.53
Advanced lung disease[a]	0.38	NR
Lymphoma[a]	0.46	NR

Footnote: [a]Presented HR for advanced lung disease and lymphoma are a mean average of HRs calculated from KM data adjusted to start at ages 12 and 20.
Abbreviations: HR: hazard ratio, KM: Kaplan Meier.

As shown in Table 66, changing the source data to the clinician estimate increased the ICER.

Scenario #4: Resource use reduction for manifestations with reduced severity: 25%

In the base case economic analysis, it was assumed that for patients experiencing improvement with manifestations due to leniolisib treatment, the cost of current clinical management was reduced by 50%, based on expert feedback (Section B.3.5.2). To explore the impact of this assumption, resource use was instead reduced by 25% in this scenario analysis. Making this more conservative assumption had minimal impact on the overall ICER (Table 66).

Scenario #5: No age-related utility decrements

Leniolisib is indicated from the age of 12 years and is expected to be taken life-long. Age-related utility decrements were applied within the base case to reflect a gradual decline in HRQoL with age, as seen in the general population. To explore the impact of the assumption of age-related utility decrements over a lifetime horizon, age-related utility decrements were not applied in this scenario analysis. Removing age-related utility decrements significantly reduced the overall ICER (Table 66).

Scenario #6: Source of utility data for manifestations: clinician EQ-5D vignette study

In the base case economic analysis, the utility impacts of manifestations are informed by utility values from proxy conditions. To explore uncertainty around the use of these proxy values, results of the clinician EQ-5D vignette study (see Table 64 for the results; exercise described in Section B.3.4.5) were used to inform the utility impact of each manifestation in this scenario analysis.[23, 311] This scenario led to a small increase in the overall ICER (Table 66).

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Table 64: Utility values associated with each manifestation from the clinician EQ-5D exercise (scenario analysis #7)

Manifestations	Utility, disutility or multiplier	SE
Long term impact of lymphoproliferation + splenomegaly	0.84	0.08
Gastrointestinal disorder utility multiplier	0.83	0.08
Cytopenia utility multiplier	0.95	0.09
Malignancy disutility (first year only)	0[a]	N/A
Malignancy utility multiplier (first year and beyond)	0.31	0.03
Infection disutility	-0.0066	0.00066
Bronchiectasis utility multiplier	0.76	0.08
Advanced lung disease utility multiplier[b]	0.65	0.06
Hearing loss disutility (weighted average)	-0.02	N/A

Footnotes: [a]First year of malignancy assumed to have no additional impact on utility. [b]Value aligned to base case value (Bradley et al., 2013[327]) as the utility for advanced lung disease was not assessed as part of the clinician EQ-5D survey. [c]Value aligned to base case value (Global Burden of Disease Study 2019[325]) as the utility for hearing loss was not assessed as part of the clinician EQ-5D survey.
Abbreviations: N/A: not applicable; SE: standard error.
Sources: Pharming Data on File, 2023.[311]

Scenarios #7 and #8: Baseline utility

In the base case economic analysis, 'baseline' utility (i.e. utility levels in the absence of any manifestations and treatments) was informed by the utility estimated for the baseline APDS disease state from the EQ-5D vignette valuation exercise (Section B.3.4.5). To explore uncertainty associated with the choice of baseline utility, two scenario analysis were conducted.

In **scenario #7**, baseline utility was informed by data from Study 2201 Part II. Baseline SF-36 data from Study 2201 Part II were mapped to EQ-5D-3L utilities using the mapping algorithm reported by Rowen et al., 2009. Rowen et al. mapped SF-36 scores onto the EQ-5D index using a number of different model specifications and compared predicted EQ-5D scores for subsets of the sample across inpatient and outpatient settings and medical conditions. The study adhered to DSU TSD12 recommendations, testing overlap of domains and reporting results of statistical fits.[313] Model 3 outperformed other models in the Rowen et al., 2009 study, as well as other published models (providing most accurate predictions), and was therefore used in this mapping exercise.[337]

Baseline SF-36 data from Study 2201 Part II were chosen to inform HRQoL in the scenario analysis, over the other trials, because:[17, 27, 35]

- At Study 2201E1 Baseline, a substantial proportion of patients had already been receiving leniolisib in Study 2201
- Study 2201 Part II had a larger sample size than Study 2201 Part I, making the baseline data more relevant for decision-making

As mentioned in Section B.3.4.1, the impact of lymphoproliferation on HRQoL was reflected in the baseline SF-36 data from Study 2201 Part II, and therefore baseline SF-36 data could not inform baseline HRQoL in the model base case, but instead was used in a scenario analysis. Within this scenario analysis, to avoid double counting the impact of manifestations, a regression

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analysis was conducted to estimate the baseline utility for individuals without manifestations. The regression analysis included EQ-5D-3L index score as the response variable and number of QoL-limiting factors in medical history as the explanatory variable, and resulted in the derivation of the mapped baseline utility of 0.85 for no QoL-limiting factors (see Table 65; presented alongside utility value derived from all trial participants). The baseline EQ-5D utility score included within scenario #9 therefore estimates the HRQoL of people with APDS presenting without any manifestations.

Table 65. Mapped baseline EQ-5D-3L index scores

Population	N	Mean	SE	95% CI	Range
All participants	39	0.784	0.0216	0.741, 0.826	0.485–0.974
Trial participants without acute manifestations and not undergoing any major treatments/surgeries	31	0.85	0.0301	0.733, 0.851	-

Abbreviations: CI: confidence interval; SE: standard error.

In **scenario #8**, general population utility values were calculated for each cohort (i.e. each starting age) using methods set out by Ara and Brazier, 2010.[338] For example, at age 12, the general population utility was estimated as 0.983 (SE: 0.09) [numerical data available within model].

These scenarios led to minimal changes to the ICER (Table 66).

Scenario #9: Utility impact reduction for manifestations with reduced severity: 25%

In the base case economic analysis, it was assumed that for patients experiencing improvement in severity of manifestations due to leniolisib treatment, the utility decrement due to those manifestations would be reduced by 50%, based on expert feedback (Section B.3.4.5; utility impact of leniolisib). To explore the impact of this assumption, the utility decrement was instead reduced by 25% in this scenario analysis, as a more conservative assumption. This scenario led to a small increase in the ICER (Table 66).

Scenario #10: Clinician estimate of discontinuation rate

In the base case of the model, the annual rate of discontinuation of leniolisib is informed by the rate of discontinuations across Study 2201, Study 2201E1 and the leniolisib EAP (Section B.3.3.6). A question around treatment discontinuation was included in the quantitative survey of the Expert Consultancy project (Exercise 4). Clinicians were asked to estimate the proportion of patients receiving a PI3Kδ-specific inhibitor that they would expect to discontinue treatment at any point, and for any reason. The mean response was 14%, and no clinicians expected treatment discontinuation due to lack of effectiveness.[14]

Therefore, this scenario analysis assessed the impact of applying this 14% per patient-year discontinuation rate. This change in discontinuation rate led to a small increase in the overall (Table 66).

Results of the scenario analyses

Deterministic results of each scenario analysis are presented in Table 66. For all results, leniolisib has been included at proposed PAS price and the comparator at list prices. QALY-weighted ICERs range from £[redacted] to £[redacted] per QALY gained, with eight of the ten scenarios having ICERs within 10% of the base case. The highest ICER was in the scenario using clinician

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estimates of leniolisib efficacy for each manifestation from the modified SEE, rather than using data from the clinical trials and EAP. This indicates that the base case ICER is robust to various data sources and assumptions around model inputs.

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Table 66: Results of the deterministic scenario analyses (with QALY weighting and proposed PAS)

#	Scenario description	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		[redacted]	10.46	[redacted]
1	Manifestation-specific mortality	[redacted]	10.18	[redacted]
2	Source of manifestation rates under current clinical management: modified SEE clinician estimate	[redacted]	10.26	[redacted]
3	Impact of leniolisib on manifestations: modified SEE clinician estimate	[redacted]	8.51	[redacted]
4	Resource use reduction for manifestations with reduced severity: 25%	[redacted]	10.46	[redacted]
5	No age-related utility decrements	[redacted]	11.01	[redacted]
6	Source of utility data for manifestations: clinician EQ-5D vignette study	[redacted]	9.95	[redacted]
7	Source of baseline utility: Study 2201 Part II (SF-36 mapped to EQ-5D-3L)	[redacted]	10.24	[redacted]
8	Source of baseline utility: general population estimate	[redacted]	10.52	[redacted]
9	Utility impact reduction for manifestations with reduced severity: 25%	[redacted]	9.97	[redacted]
10	Clinician estimate of discontinuation rate	[redacted]	5.14	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

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B.3.11 Subgroup analysis

As explored in Section B.2.7,B.2.7, Study 2201 Part II and Study 2201E1 investigated the impact of leniolisib in people with both subtypes of APDS (APDS1 and APDS2).[37, 38] Results of the co-primary endpoints of Study 2201 Part II in the overall populations were generally consistent across subgroups defined by genetic diagnosis (APDS1 vs APDS2), age group (<18 years vs ≥18 years) and sex (female vs male);[37, 42] see Appendix E for individual subgroup analyses for clinical efficacy.

Given that people with APDS1 and with APDS2 are expected to respond similarly to leniolisib, separate economic results have not been presented for APDS1 and APDS2.

B.3.12 Benefits not captured in the QALY calculation

Leniolisib treatment is associated with a number of benefits which are not captured in the QALY calculation.

Clinical benefits

As discussed in Section B.1.4.2, expression and activity the PI3Kδ enzyme complex has also been reported in non-immune cells,[49-51] and may play a role in neurodevelopment, allergies and asthma in individuals with APDS.[10, 12, 13, 156, 157] As these manifestations are not included in the model based on lack of available evidence, the benefit of leniolisib may be underestimated.

Benefits to individuals' work and education

APDS is expected to be associated with a substantial societal burden due to individuals missing work and/or school due to illness and hospitalisation, in addition to productivity losses. However, the economic model in this evaluation adopted an NHS and PSS perspective rather than a societal perspective, in line with the NICE reference case. An additional instrument assessed in the leniolisib clinical trials was the work productivity and activity impairment (WPAI) plus classroom impairment questionnaire (CIQ) [WPAI-CIQ].[37, 38, 44] During Study 2201, participants treated with leniolisib reported an increase from Baseline in the hours worked and hours of class, maintained throughout Study 2201E1.[37, 38, 44] Findings from the pivotal clinical trial, Study 2201 Part II, also observed improvements from Baseline (decrease) in the impairment experienced by individuals with APDS whilst working (mean CfB of -17.78 at Week 12, [n=9]) due to health.[37] These results may have been impacted by the COVID-19 pandemic however, thematic analysis of available qualitative evidence (including patient narratives from the leniolisib clinical trials) supplements these data reporting that improvements in work/school performance/attendance (13.9%) were explicitly attributed to leniolisib treatment.[284]

In addition, leniolisib may impact the motivation and financial earnings of individuals with APDS at work. One study interviewing people with IEIs requiring IRT in the UK noted several indirect costs including travel costs and loss of earnings; individuals felt that they were unable to fulfil employment requirements or push forward in their careers, leading to long-term financial consequences for patients if they were unable to work or hard to reduce hours.[339]

Overall, the potential benefits of leniolisib with respect to hours worked/class attended, and hence the broader societal value of leniolisib, has not been captured in the economic model.

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Burden to the NHS benefits

Leniolisib treatment is expected to reduce the need for IRT in individuals with APDS, diminishing the burden of IRT on patients and the NHS,[52] for example, by reducing the amount of time spent in hospital receiving invasive IRT transfusions,[31] supply chain easing[198] and reducing the risk of the transfer of new infections and disease from this blood-derived product.[54] Moreover, in times of IRT shortage, a reduction of individuals with APDS on IRT may provide a wider societal benefit that is not captured by the QALY.

As described in Section B.1.4.3, the long-term and high frequency use of antimicrobials in combination with continued infections may contribute to antimicrobial resistance.[58] Findings from the leniolisib clinical trials demonstrate that continued treatment with leniolisib reduces the need for antibiotics, and in turn, the incidence of individuals who present with antimicrobial-resistant infections is expected to concordantly decrease.[56-58] These benefits to the NHS and wider society are not captured in the QALY calculation.

Additionally, the NHS England Medicines Optimisation Executive Group (MOEG) has identified and agreed 16 national medicines optimisation opportunities for the NHS in 2023/24. One key objective is related to enhancing productivity and value for money.[249] Rituximab is administered by intravenous infusion over a few hours, on each occasion, through a two-dose course of treatment with a two-week internal between doses. This creates capacity challenges for the NHS. Reducing the need for rituximab could present an opportunity to increase productivity within hospitals by freeing hospital beds and staff time.

Caregiver HRQoL benefits

Many people with APDS require physical and emotional support from caregivers who may, in turn, be impacted by the stress of caring for individuals with APDS.[11] As discussed in Section B.2.6, leniolisib treatment can lead to a reduction in the frequency and severity of manifestations associated with APDS and therefore, positively impact caregiver HRQoL. For example, IVIG infusions can last approximately two to four hours with a follow-up of up to four hours, which is to be repeated every 3–4 weeks.[31] Hence, patients and caregivers may spend long periods of time travelling to and from infusion sites.

Caregivers may need take time off from work to take care of or home-school their dependent. As a targeted therapy, leniolisib would be expected to have long-term benefits, preventing the progression of manifestations and improving symptoms. For example, after treatment with leniolisib, home-schooled patients showed improvements in energy levels and tolerance of physical activity,[37] which may allow the patient to be more independent, alleviating the burden on caregivers.

UK Rare Disease Strategy

Patients with APDS currently have no nationally commissioned treatment pathway, which may lead to inconsistency in care across the APDS population in the UK. In line with the UK Rare Disease Strategy,[59] leniolisib would provide an effective treatment option, promoting equitable access across the licensed APDS population in the UK.

Leniolisib further supports the UK Rare Disease Strategy by offering a highly evidence-based treatment approach, compared with current treatment options which have not been assessed through clinical trials. Given the recognition of APDS as recently as 2013,[2] providing patients with

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access to leniolisib would allow delivery of rapid and effective transformations of research and advances in understanding into clinical care.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

Conceptual validation

The de novo model was developed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Modelling Practices,[340] and in keeping with the recommendations outlined in the NICE reference case. The model structure underwent conceptual validation via one-to-one interviews with three HTA experts representing Europe and Canada, as well as one UK clinical expert.

Technical validation

In alignment with best practice, validation of the economic model structure was conducted by separate, independent health economist experts, not previously involved in the model conceptualisation or programming. Once fully developed, the model underwent two independent quality control and technical validation processes which included checking of all model calculations including standalone formulae, equations and Excel macros programmed in VBA. The correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks) were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

Clinical validation

Extensive clinical validation was undertaken to inform and validate the assumptions included within the base case cost-effectiveness analysis, as detailed throughout Section B.3. The Expert Consultancy gathered expert judgement from nine clinical experts, utilising a mixed methods approach. Both qualitative (expert opinion) and quantitative (expert elicitation) information was collected; expert elicitation was collected using structured and unstructured methods, depending on the quantities of interest.[14]

B.3.14 Interpretation and conclusions of economic evidence

Summary of the cost-effectiveness results

Leniolisib was associated with increased health benefits compared with current clinical management of 15.46 weighted QALYs, in alignment with the clinical and HRQoL improvements observed with leniolisib in the clinical trials. Overall, leniolisib was found to be plausibly cost-effective compared with current clinical management at a willingness-to-pay threshold of £100,000/QALY, yielding an ICER of £[redacted]/QALY.

Strengths and limitations of the cost-effectiveness analysis

The de novo model was developed in line with the decision problem and with an NHS and PSS perspective, with direct health effects on adults and adolescents with APDS considered over a lifetime horizon and costs and benefits annually discounted at a rate of 3.5% and 1.5%,

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respectively. Appropriate UK inputs were used where possible and appropriate (e.g. unit costs were sourced from NHS reference costs, PSSRU costs and the BNF).

The model underwent technical, conceptual and clinical validation to ensure that it captured the key aspects of living with APDS. Many of the key assumptions regarding the model structure and inputs were validated by the Expert Consultancy project, which included clinicians in the UK, and were robustly explored across ten different scenario analyses (see Section B.3.11).

Strengths of the analysis include the following:

- To accurately capture the key aspects of APDS, a simple cohort model with each manifestation and treatment modelled with a partitioned approach was deemed the most appropriate approach (see Section B.3.2.2 for further justification); this approach was validated by three HTA experts and one UK clinical expert
- The economic model for leniolisib adopted a lifetime horizon to ensure full costs and health benefits were captured
- In the base case economic analysis, the age-specific manifestation and treatment rates in the current clinical management arm were informed by cohort of individuals with APDS in the ESID registry, which is the largest registry for individuals with PIDs globally[6, 13, 43, 65, 66]
- Findings from the modified SEE in the Expert Consultancy (Exercise 1) which involved five clinical experts (including 2 from the UK) validated the manifestation and treatment rate data from the ESID registry in the economic model[14]
- A collective body of evidence on the benefit of leniolisib treatment was considered in order to robustly model the impact of leniolisib on APDS manifestations. Evidence included results from the leniolisib clinical trials (the RCT, Study 2201, as well as up to six years of data from the OLE, Study 2201E1), the global EAP with 72 patients having received treatment with leniolisib and the modified SEE from the Expert Consultancy (Exercise 1)[17, 27, 35, 64, 282]

Limitations of the analysis include the following:

There was a limited availability of data specifically for APDS, which is common in the study of ultra-rare diseases. Therefore, available evidence may not have fully captured the impacts of APDS and leniolisib on clinical outcomes and costs. Evidence from a number of different sources, as well as assumptions, were used in the economic model.

- Where there was a lack of clinical data on the impact of leniolisib, data were sourced from a robustly conducted modified SEE (Expert Consultancy, Exercise 1)
- Given the lack of utility data specific to APDS, utilities from proxy conditions and a vignette study were used to populate the economic model, giving rise to uncertainty in the modelling of HRQoL.
- Overall survival data from the Pharming case series did not span a lifetime horizon.[117] Therefore, extrapolations were necessary and aligned with the results of clinical validation. Additionally, this dataset may be biased towards reporting information from surviving patients, so the use of this dataset forms a conservative approach

Conclusion

In APDS, the combination of immune dysregulation and immune deficiency in APDS can lead to early mortality and severely impair patient HRQoL.[11, 21-25] There are currently no licensed treatments available for APDS in the UK. Consequently, individuals receive multiple symptomatic

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treatments in an attempt to manage individual manifestations, and the combination of immune dysregulation and immune deficiency.[3, 13, 14, 17, 18, 27, 28] Despite current clinical management, individuals with APDS continue to experience disease progression and life-threatening manifestations, resulting in a reduced life expectancy compared with people without APDS.[3, 12, 13, 15, 18]

Leniolisib is the first and only targeted disease-modifying therapy for individuals with APDS,[167] selectively inhibiting p110δ in the hyperactive PI3Kδ enzyme complex. By normalising the PI3Kδ pathway, 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, all of which is expected to substantially reduce mortality and improve HRQoL.

The results of the base case cost-effectiveness analysis demonstrate that leniolisib (with proposed PAS) is associated with increased health benefits versus current clinical management over a lifetime horizon, and was found to be plausibly cost-effective compared with current clinical management at a willingness-to-pay threshold of £100,000/QALY, yielding an ICER of £[redacted]/QALY. A range of scenario analyses were conducted to test the robustness of the model results to alternative model inputs and assumptions. QALY-weighted ICERs ranged from £[redacted] to £[redacted] per QALY gained, with eight of the ten scenarios having ICERs within 10% of the base case, where the highest-ICER scenario used efficacy assumptions based on expert opinion rather than clinical trial and observational data. This indicates that the base case ICER is robust to various data sources and assumptions around model inputs. Additionally, in the PSA, leniolisib had a [redacted]% chance of remaining cost-effective at a willingness to pay threshold of £100,000 weighted QALY gained. Given that clinical trial data, real-world evidence and modified SEE data were generalisable to UK clinical practice, as well as the validation of the modelling approach by clinical experts in the UK and the use of UK cost and resource inputs, the model and its results are considered to be generalisable to clinical practice in England.

B.3.15 Cost to the NHS and Personal Social Services

Eligible population

APDS is an ultra-rare condition, with recent literature reporting that APDS affects between 1–2 per 1,000,000 individuals globally.[4] In alignment with this estimate, there are [redacted] patients (of all ages) with APDS currently enrolled in the UKPID registry in England (as of 30th April 2024).[161] The English clinical immunology community acknowledges that multiple patients with APDS have died over the past five years, including some individuals never included within the registry. [redacted] this leads to an expected total of [redacted] patients in England (see Table 67). Of these patients, [redacted] are believed to be aged 12 years and older.

Based on the anticipated positioning of leniolisib (described in Section B.1.4.3), all newly diagnosed individuals would be eligible for treatment with leniolisib. However, [redacted]. Therefore, as outlined in Table 67 the anticipated eligible population in Year 1 totals [redacted] patients.

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Table 67: Summary of epidemiological inputs in the budget impact analysis (for Year 1)

Item	Input	Source	Example calculation: resultant number of individuals in Year 1 (2025)
Total population of England	57,106,398	ONS mid-2022 estimate (England)[341]	-
Annual population growth rate	1.00%	ONS mid-2022 estimate (England)[341]	58,836,779
Estimated prevalence of APDS in England	[redacted]	[redacted]	[redacted]
Proportion of patients aged 12 years and older	[redacted]	[redacted]	[redacted]
Proportion eligible for treatment with leniolisib [redacted]	[redacted]	[redacted]	[redacted]
Annual increase in number of incident diagnosed cases of APDS, following the positive recommendation of a PI3Kδ-specific inhibitor by NICE	Year 1: 2.50 Year 2: 3.83 Year 3: 5.50 Year 4: 6.83 Year 5: 8.83	Expert Consultancy (Exercise 4)[341]	[redacted]

Abbreviations: APDS: activated PI3K delta syndrome, DCO: data cutoff, ONS: Office for National Statistics; UKPID: UK Primary Immunodeficiency (registry).

It is believed that some individuals, particularly adults presenting to clinicians prior to 2021, may not have had a genetic test and so have been managed with the less specific diagnosis of CVID. Consequently, as part of the Expert Consultancy project (Exercise 4, Quantitative), clinical experts were asked to estimate the increase in incident diagnosed cases of APDS per year in England (across all ages), following the positive recommendation of a PI3Kδ-specific inhibitor by NICE. The mean estimates are provided in Table 67,[14] and were included in the calculation of the total eligible population for leniolisib in England each year, as shown in Table 68. It was assumed that 65% of those incident patients would be aged 12 years and older, and would therefore be eligible for treatment with leniolisib.

Table 68: Individuals with APDS eligible for treatment with leniolisib

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Total number of individuals with APDS, who have not recieved HSCT, and therefore would be eligible for treatment with leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: APDS: activated PI3K delta syndrome.

Expected uptake

As part of the Expert Consultancy (Exercise 4, Quantitative), clinical experts were asked to predict the uptake of a PI3Kδ-specific inhibitor in eligible people with APDS, for the first five years

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after a positive NICE recommendation. The mean results are presented in Table 69. Specifically, it was noted that uptake was likely to increase with individual and physician confidence, particularly as a PI3Kδ-specific inhibitor would be the only specific treatment for APDS, with few significant side effects as compared with current immunosuppressive treatment.[14]

Table 69: Market share estimates

Technology	Scenario without leniolisib	Scenario with leniolisib				
		Year 1	Year 2	Year 3	Year 4	Year 5
Leniolisib	0%	78%	83%	88%	90%	90%
Current clinical management (alone)	100%	22%	18%	13%	10%	10%
Total	100%	100%	100%	100%	100%	100%

Source: Expert Consultancy, Exercise 4 (Quantitative).[14]

Costs and resource use

As an oral therapy, no additional costs are associated with the administration of leniolisib, beyond acquisition costs.

The anticipated label for leniolisib in the UK indicates that [redacted]. However, in the Expert Consultancy (Exercise 4), clinicians estimated that the proportions of people attending monitoring visits, and frequencies of attendance, would be reduced for people receiving leniolisib versus current clinical management.[14] The potential cost savings associated with leniolisib treatment due to a decreased need for monitoring visits have been considered within the cost-effectiveness analysis (see Section B.3.5.2).

Costing of treatments in the budget impact analysis was aligned with that of the de novo cost effectiveness analysis. A summary of the total costs per person per year for each cost category included in the budget impact analysis is presented below in Table 70. Please note that these are the disaggregated costs associated with each treatment option.

Table 70: Costs of treating manifestations

Manifestation	Cost (£ per person per year)	
	Leniolisib	Current clinical management
Lymphoproliferation	No associated cost	
Infections	See 'Antimicrobials' in Table 71	
Gastrointestinal manifestations	238.81	589.74
Malignancies	2,719.82	3,732.54
Cytopenia	481.42	1,073.44
Bronchiectasis-associated airway disease	6,895.99	8,813.65
Advanced lung disease	320.43	2,749.70
Hearing loss	35.72	80.86

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Table 71: Current clinical management treatment costs

Cost		Cost (£ per person per year)	
		Leniolisib	Current clinical management
Antimicrobials	Year 1	206.27	229.91
	Year 2	202.57	229.91
	Year 3	190.66	229.91
	Year 4	[redacted]	[redacted]
	Year 5	[redacted]	[redacted]
IRT	Year 1	12,924.82	18,873.02
	Year 2	13,605.48	18,873.02
	Year 3	13,802.29	18,873.02
	Year 4	7,550.98	18,873.02
	Year 5	[redacted]	18,873.02
Steroids		0.16	0.37
Immunosuppressants		0.00	536.90
HSCT		18,644.39	30,999.42
Tonsillectomy		1,055.62	1,081.04

Abbreviations: HSCT: haemopoietic stem cell transplantation, IRT: immunoglobulin replacement therapy.

Benefits and savings

The main clinical benefits leading to resource savings for the NHS that may be expected from using leniolisib have been captured within the budget impact analysis. However, additional benefits to the NHS are described below.

- As discussed in Document B Section B.1.4.2, expression and activity the PI3Kδ enzyme complex has also been reported in non-immune cells,[49-51] and may play a role in neurodevelopment, allergies and asthma in individuals with APDS.[10, 12, 13, 156, 157] As these manifestations are not included in the model based on lack of available evidence, the benefit of leniolisib may be underestimated
- Leniolisib treatment is expected to reduce the need for IRT in individuals with APDS, diminishing the burden of IRT on patients and the NHS,[52] for example, by reducing the amount of time spent in hospital receiving invasive IRT transfusions,[31] supply chain easing[198] and reducing the risk of the transfer of new infections and disease.[54] Moreover, in times of IRT shortage, a reduction of individuals with APDS on IRT may provide a wider societal benefit that is not captured by the QALY.
- As described in Section B.1.4.3, the long-term and high frequency use of antimicrobials in combination with continued infections may contribute to antimicrobial resistance.[58] Findings from the leniolisib clinical trials demonstrate that continued treatment with leniolisib reduces the need for antibiotics, and in turn, the incidence of individuals who present with antimicrobial-resistant infections is expected to concordantly decrease.[56-58] These benefits to the NHS and wider society are not captured in the QALY calculation.
- Additionally, the NHS England Medicines Optimisation Executive Group (MOEG) has identified and agreed 16 national medicines optimisation opportunities for the NHS in 2023/24. One key objective is related to enhancing productivity and value for money.[249] Rituximab is administered by intravenous infusion over a few hours, on each occasion, through a two-dose course of treatment with a two-week internal between doses. This

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creates capacity challenges for the NHS. Reducing the need for rituximab could present an opportunity to increase productivity within hospitals by freeing hospital beds and staff time

- Results of the Expert Consultancy project (Exercise 4, Quantitative) indicate that the frequency of visits to specialists would decrease upon initiation of leniolisib and further decrease upon stabilisation of disease.[14] It is expected that monitoring costs would therefore decrease, in line with reductions in manifestations, with long-term leniolisib treatment. However, the budget impact analysis conservatively modelled no change in monitoring costs for both individuals treated with leniolisib and the relevant comparator

Estimated annual budget impact

The expected budget impact due to the introduction of leniolisib in NHS England as a treatment for adults and adolescents aged 12 years and older, in line with the final NICE scope for this appraisal, is summarised in Table 72.

Table 72: Expected budget impact (with anticipated PAS for leniolisib)

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Eligible population for treatment with leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway in scenario without leniolisib (£)	1,486,947.89	1,658,127.39	1,903,946.52	2,209,209.19	2,603,860.63
Cost of treatment pathway in scenario with leniolisib (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The net budget impact associated with the introduction of leniolisib is not expected to exceed the budget impact test threshold of £20 million per year in any of the first 3 years of its use in NHS England.

Limitations of budget impact assessment

Due to the ultra-rare nature of APDS, it was necessary to make several assumptions in the budget impact analysis:

- Efficacy and safety from the leniolisib clinical trials, EAP survey and Expert Consultancy (Exercise 1) can be generalised to the UK clinical setting[14, 17, 27, 35, 64]
- Where multiple subtypes of manifestations could inform the model (e.g. lymphoma, autoimmunity) a representative manifestation subtype was chosen based on prevalence
- A 50% reduction in the costs associated with manifestations was assumed for individuals experiencing a reduction in severity of these manifestations

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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]

Summary of Information for Patients (SIP)

June 2024

File name	Version	Contains confidential information	Date
ID6130_Leniolisib in APDS_SIP_07Jun2024	1.1	No	07Jun2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **blue**.

1a) Name of the medicine (generic and brand name):

Generic name: Leniolisib; **brand name**: Joenja®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

Leniolisib will be used for the treatment of **activated phosphoinositide 3-kinase delta syndrome** (**APDS**), in adults and adolescents who are 12 years of age and older.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **Medicines and Healthcare products Regulatory Agency** (**MHRA**) is reviewing whether leniolisib should be approved and granted **marketing authorisation** as a

treatment for APDS. The marketing authorisation for leniolisib is therefore pending. More information on this can be found in **Document B** in **Section B.1.2**.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below summarises the patient advocacy organisations which Pharming have collaborated with from 2023 onwards, and how Pharming engages or financially supports these charities. Financial support varies from supporting workshops to developing patient stories for internal projects/public websites. Prior to 2023, Pharming provided a donation to Immunodeficiency UK, towards the development of patient stories for Diagnosis Day and the addition of information about APDS (and the patient stories) on their website.

Patient group	Engagement/activity with each group	Financial support provided
International Patient Organisation for Primary Immunodeficiencies (IPOPI)	Web-based medical education event – October 2023	€15,000.00 (EUR)
	International Primary Immunodeficiencies Congress sponsorship, stand and medical education symposium – November 2023	€55,625.00 (EUR)
	Asian IPOPI meeting sponsorship – March 2024	€60,000.00 (EUR)
Beacon for Rare Diseases	Sponsorship for a genetic diagnostic workshop for patient organisations, paid on the 6th May 2024	£19,179.99 (GBP)
	Invited to sponsor a patient organisation networking event.	N/A

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The condition that leniolisib is intended to treat is APDS

What is APDS?

APDS is one of a group of conditions called **primary immunodeficiencies (PIDs)**.[1] It is also referred to as an **inborn error of immunity (IEI)**.[2] Both terms mean that APDS affects the body's **immune system** so it cannot work correctly.[2] The immune system is the body's defence against anything that it recognises as '**non-self**', such as outside invaders (e.g. bacteria and viruses which can cause infections) and abnormally growing and/or infected cells.[3]

Individuals with APDS experience multiple **manifestations** at the same time. Together, these manifestations have a substantial negative impact on patient **quality of life**.[2, 4-6] Ultimately, the manifestations of APDS can also lead to a shortened life, sometimes due to cancer.[7-10] Please refer further below in **Section 2a** for more information on how APDS impacts a person's life expectancy and the disease burden of APDS.

What causes APDS?

APDS was first recognised as a unique disease in 2013 and is an ultra-rare **genetic condition**.[11, 12] It is caused by changes in APDS-relevant **genes**; these changes are otherwise known as **disease-causing gene variants**.[1]

Disease-causing variants in APDS-relevant genes result in overactivity of a **protein** called PI3K delta **(phosphoinositide 3-kinase delta)**. PI3K delta is found in many different cells, including **white blood cells** (WBC) in the immune system. PI3K delta sends out signals to control how WBCs develop and mature. Therefore, when PI3K delta is overactive, some types of WBCs do not develop or mature properly. This means that people with APDS do not produce normal numbers of different healthy WBCs. People with APDS may produce too few of some types of WBC and/or too many of other types of WBC. As a result, the immune system cannot work correctly.[1, 2, 13]

B cells are a type of WBC that can be activated when anything 'non-self' is detected in the body.[14] People with APDS usually have a low number of **naïve B cells**.[15] These are B cells that have not yet been activated by anything 'non-self' in the body. When B cells are activated they produce **antibodies**, which are substances that help the immune system to fight off anything that it recognises as 'non-self', such as bacteria and viruses.[14] People in the **general population** (i.e. those who do not have APDS) produce five different types of

antibodies.[16] However, people with APDS do not produce enough of some antibody types.[13]

Who can get APDS?

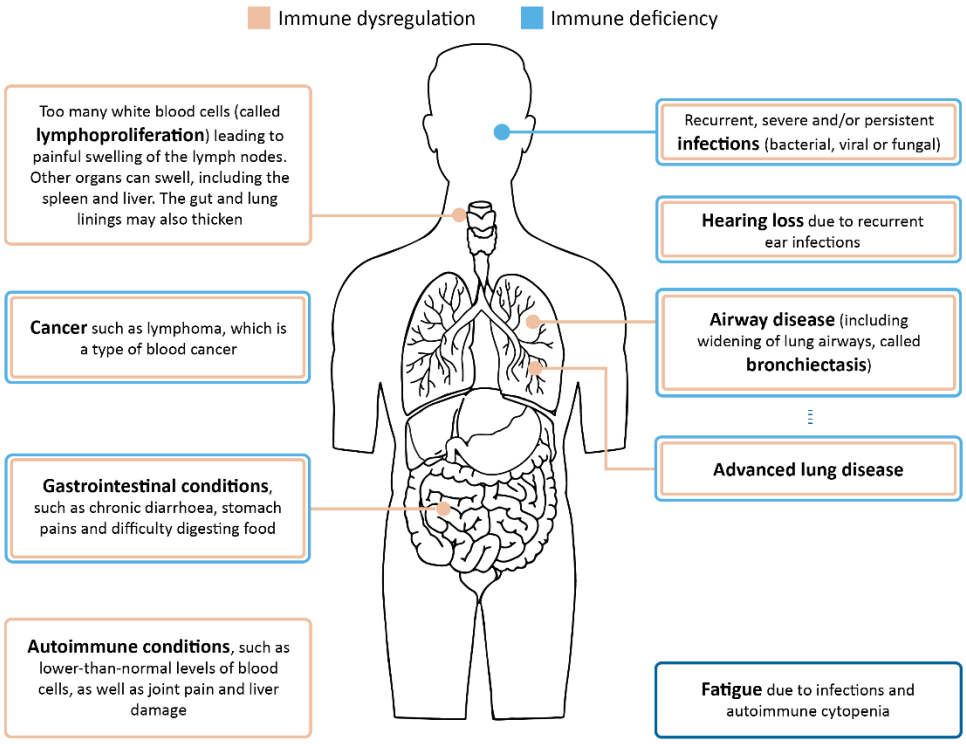
Disease-causing gene variants can be passed on from one generation to the next. This means APDS can be inherited from either parent. Disease-causing gene variants can also develop randomly when neither parent has the disease. This means anyone can have APDS, regardless of sex.[17]

How many people have APDS?

At the moment, between 1–2 individuals out of every one million people are known to live with APDS.[6]

What are the manifestations of APDS?

As the immune system cannot work correctly, people with APDS experience lots of different manifestations, making it a complex condition. The diagram below shows how APDS can affect the body in many ways. Some people with APDS might only experience a few manifestations, while others might experience multiple manifestations.[13]

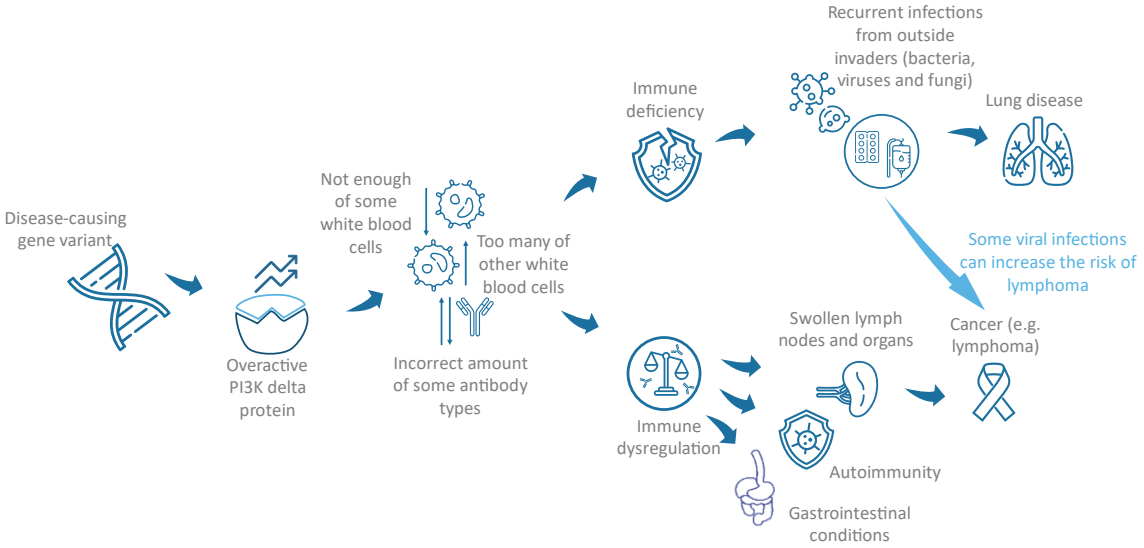


Source: Büsch et al., 2023,[18] Coulter et al., 2017,[9] Coulter et al., 2018,[13] Jamee et al., 2019,[10] Maccari et al., 2023,[2] Pharming Data on File,[19] Pharming Data on File, 2023,[20] Rao et al., 2023.[21]

There are two main ways in which the immune system in people with APDS no longer works correctly. Firstly, APDS causes **immune dysregulation**, which can cause specific organs to swell, or lead to **autoimmunity** where the immune system mistakenly attacks the body's own healthy **tissues** or organs.[13] Secondly, APDS also causes **immune**

deficiency, which means the body doesn't fight outside invaders (e.g. bacteria and viruses which can cause infections) and abnormally growing and/or infected cells as effectively as it does for people in the general population.[13]

The figure below shows how immune dysregulation and immune deficiency in APDS lead to the manifestations experienced by affected individuals.



Source: Coulter et al., 2017,[9] Coulter et al., 2018,[13] Maccari et al., 2023,[2] Mundo et al., 2020,[22] Raab-Traub et al., 2007,[23] Rao et al., 2023.[24]

Immune dysregulation

A common manifestation of APDS associated with immune dysregulation is swollen **lymph nodes** (a type of gland).[9] In the general population, lymph nodes are small, bean-shaped organs in which WBCs cluster and filter out anything 'non-self' from the body. They also house WBCs to help fight infections, and are found all around the body.[25] In APDS, the body can produce too many WBCs, which is called **lymphoproliferation**. This is a very common manifestation, occurring in approximately 86% of people with APDS.[2] WBCs can then accumulate and multiply in the lymph nodes in greater numbers than is normal, which can lead to swelling (**lymphadenopathy**). Other specific organs may also swell, including the **spleen** (**splenomegaly**) and **liver** (**hepatomegaly**).[9, 26]

People with APDS have a higher risk of developing **cancer** than people in the general population,[5] particularly in early life.[2, 10, 27] The most common cancer experienced by people with APDS is **lymphoma**.[8, 10] Lymphoma is a type of blood cancer affecting some types of WBCs.[26] When people with APDS experience lymphoproliferation, WBCs start to multiply uncontrollably and the risk of those cells becoming cancerous increases.[28, 29] Long-term infections with the Epstein-Barr virus in people with APDS may also increase the risk of lymphoma.[22, 23]

People with APDS may also experience manifestations associated with their stomach and intestines (**gastrointestinal**). This can include chronic diarrhoea, **inflammation** of the

colon (the largest part of the large intestine) and difficulty digesting and absorbing nutrients from food.[26, 30]

Immune dysregulation in people with APDS can also cause autoimmunity. This refers to when the immune system mistakenly attacks the body's healthy tissues and organs. This can lead to **cytopenia** (a lower-than-normal number of any type of blood cell), such as **anaemia** (a low number of **red blood cells**), as well as joint pain and liver damage.[9, 26, 31, 32]

Immune deficiency

Immune deficiency in APDS means that affected individuals do not have enough healthy WBCs to protect the body from outside invaders (e.g. bacteria and viruses which can cause infections). This means people with APDS get infections more frequently than people in the general population, which can range from a cold to severe illnesses. Some infections can be difficult to treat and may never completely go away. Recurrent infections of the lung, **sinuses** and/or ears are the most common manifestations of APDS.[2, 8, 9, 31, 33, 34] Repeated infections can damage the lungs and airways, and can lead to long-term lung damage and permanent hearing loss.[35] For example, people with APDS often develop **bronchiectasis-associated airway disease**,[28] which causes lots of mucus, coughing, coughing up blood, wheezing and other breathing problems.[26, 36, 37] Patients with more severe lung damage may develop **advanced lung disease**,[28] which can lead to the patient needing machines to support their breathing.[26]

There are a lot of other manifestations of APDS, like low energy, allergies and asthma.[10, 38] Children with APDS may also take longer to reach developmental milestones than other children (**developmental delay**). For example, children with APDS may start to talk later than normal.[2, 9]

How does APDS progress over time?

The manifestations of APDS typically start in early childhood (even if APDS hasn't been specifically diagnosed this early), and the first sign is usually recurrent infections. These childhood infections are usually in the lungs, sinuses and/or ears.[9, 31] About 70% of children with APDS experience manifestations by the time they are five years old. By 10 years of age, 90% of children with APDS have experienced manifestations.[39]

As people with APDS grow older, they experience more manifestations, and this worsening of the disease is called **disease progression**. The manifestations can also get more severe and can lead to irreversible end-organ damage (such as advanced lung disease and/or hearing loss) and lymphoma.[9] Around 78% of people with APDS experience lymphoma by the age of 40.[30]

How does APDS impact a person's life expectancy?

Ultimately, the manifestations of APDS often lead to premature death. Up to two out of five deaths in APDS are caused by lymphoma, but other APDS manifestations and treatments may also contribute to premature death.[7-10] There has not been enough research performed to date in order to be able to say what the life expectancy is for people with

APDS. However, survival studies have shown that 68% of people are still alive at age 40 and 70% of people are still alive at age 45.[40, 41] Since APDS was only discovered a short time ago,[12] it is possible that some people have historically died without the underlying APDS being diagnosed.

What is the impact of APDS (disease burden)?

Impact on people with APDS

The disease manifestations impact the quality of life of people with APDS. Individuals with APDS experience multiple manifestations at the same time, which add up to have a substantial negative impact on patient quality of life.[2, 4-6] People with APDS also face demanding treatment plans, including lengthy, repeated hospital stays for invasive procedures.[2, 13, 30, 42-44] Despite current treatments, people with APDS still face a high risk of lymphoma early in life, and a high risk of premature death.[2, 10, 27, 40] Living with APDS therefore has broad and substantial emotional impacts on people with APDS, leading to anxiety, depression and stress, and also affecting their ability to perform daily activities, work and/or participate in education.[45-48] The impacts are summarised from the patient perspective in **Section 2d**.

People with APDS who are diagnosed with cancer face a lot of mental stress and a drop in the quality of their life, feeling anxious and isolated. On top of these emotional struggles, they also deal with physical **symptoms** like fatigue, pain, and night sweats.[48-50] See **Section 2d** for further information from a patient perspective as to how lymphoma can impact people with APDS.

As discussed earlier within **Section 2a**, people with APDS can have swollen lymph nodes and organs, because of immune dysregulation. Individuals who have a swollen spleen or liver can experience symptoms of fatigue, severe stomach pain and may bruise and bleed more easily.[51-54] The uncontrolled multiplication of white blood cells that causes this organ swelling can also cause blockages in an individuals' airways or gastrointestinal tract.[2, 55] This may result in these individuals experiencing recurrent infections, diarrhoea, trouble swallowing and/or needing surgery.[9, 47, 56-58] In addition, cytopenia (low levels of certain cell types) can have negative impacts on energy levels, and can lead to episodes of dizziness, breathlessness whilst carrying out daily activities, as well as an increased risk of bleeding and bruising compared to healthy individuals without APDS.[20, 48, 59-61] See **Section 2d** for further information from a patient perspective as to how manifestations associated with immune dysregulation can impact people with APDS.

People with APDS experience recurrent infections, with symptoms such as a persistent cough, sore throat, high fever, muscle aches and chest pain. These can have severe effects on quality of life, and hinder individuals from carrying out activities of daily living.[26, 33, 47, 48, 62, 63] Additionally, recurrent infections can lead to irreversible end-organ damage, such as in the lungs and/or ears.[9] People with APDS have reported that they experience chest pains, difficulty breathing, as well as anxiety about the lung damage that they have experienced.[47, 48] Irreversible end-organ damage in the lungs has potentially lifelong impacts on physical health and daily activities.[6, 8, 64, 65]

See **Section 2d** for further information from a patient perspective as to how manifestations associated with immune deficiency can impact people with APDS.

Impact on families and caregivers

There is a wider impact of APDS on the caregivers, family and friends of people with APDS; see **Section 2d** for information.

What is the financial cost of APDS?

Personal cost

Based on evidence from other inborn errors of immunity, and considering the manifestations and symptoms of APDS, it is expected that people with APDS and their caregivers will:[47, 48, 66, 67]

- Miss work or school due to their manifestations (or due to caregiving)
- Lose earnings
- Not fulfil their career potential
- Spend money on travel to the hospital (including to specialised treatment centres)

Cost to the healthcare system

APDS is associated with a number of varied, recurrent and/or long-lasting manifestations. Therefore, APDS requires combinations of treatments given regularly and often for a long time.[13] Some treatments require follow-up appointments, and staying in hospital for months at a time which are associated with additional costs.[2, 13, 28, 44] It is expected that APDS costs the National Health Service (NHS) a substantial amount of money per person.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is APDS diagnosed?

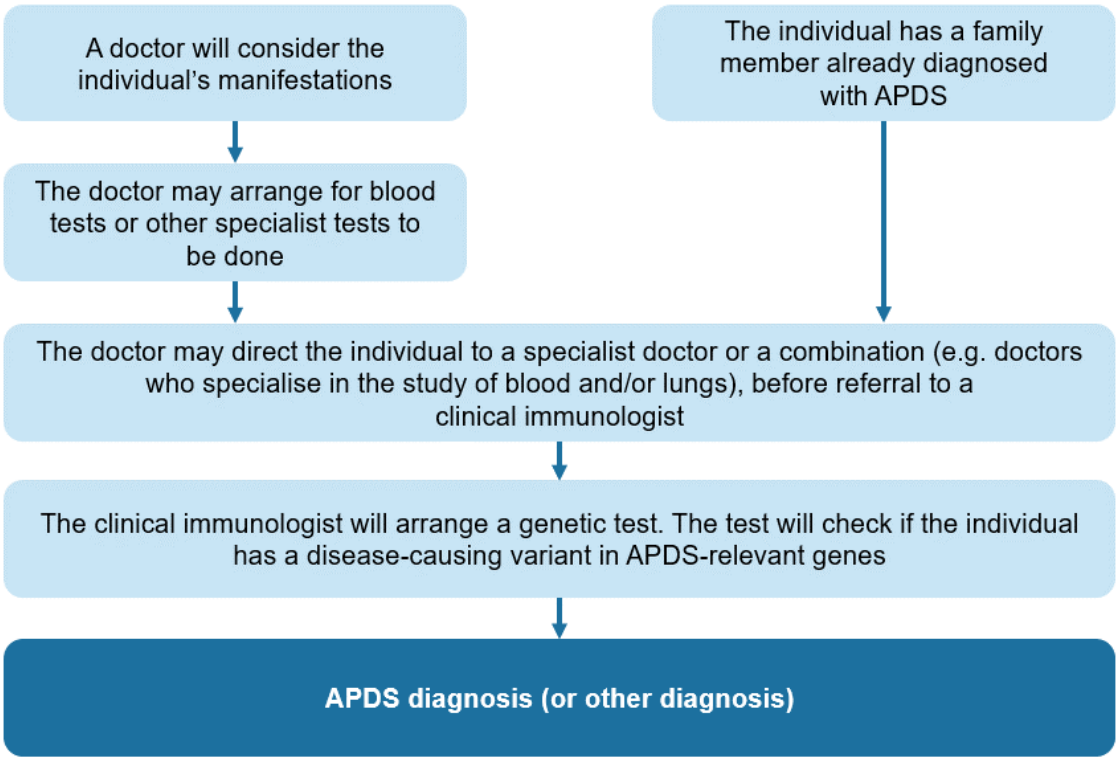
The diagram below shows how APDS is diagnosed, from when an individual first notices manifestations, and how people who have family members with APDS might get a **genetic test**.[68]

The only way to be certain of an APDS diagnosis is by doing a genetic test.[26] A genetic test is performed using a sample of saliva or blood. In the UK, a gene panel test is typically used which looks for disease-causing variants in different genes for a wide range of diseases, including APDS.[17, 69] To diagnose APDS, individuals may also have other laboratory tests, for example, counting the number of immune cells in the blood.[17, 26]

At the moment, diagnosis of APDS can take around seven years from first presentation.[10] Individuals may see several different doctors and receive many different treatments before

referral to a **clinical immunologist** (a doctor who specialises in diagnosing and treating people with immune conditions) and receiving a definitive diagnosis.[10, 70] This is because many of the earliest manifestations of APDS (such as infections of the lung, sinuses and/or ear) can present as a cold and/or cough and are experienced by lots of people in the general population.[8, 33] Therefore, individuals may not be referred to a clinical immunologist until it has been shown that these manifestations are severe, recurrent and/or persistent and cannot be treated by conventional treatments. Due to the complex nature of APDS and the many different manifestations, APDS can be difficult to diagnose for most doctors. Additionally, many doctors are not familiar with APDS because it is an ultra-rare condition and was only identified recently.[5, 12]

It is important for people with APDS to get a quick diagnosis because the earlier the diagnosis, the earlier they can receive appropriate treatment.[10, 12] Extended delays to diagnosis and treatment may allow the manifestations APDS to progress more quickly than if APDS was diagnosed earlier.[70] Disease progression can, in turn, lead to irreversible end-organ damage, such as in the lungs and/or ears, as well as an increased risk of cancer.[5, 9, 13]



Further information on APDS and how it is diagnosed is provided here.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For

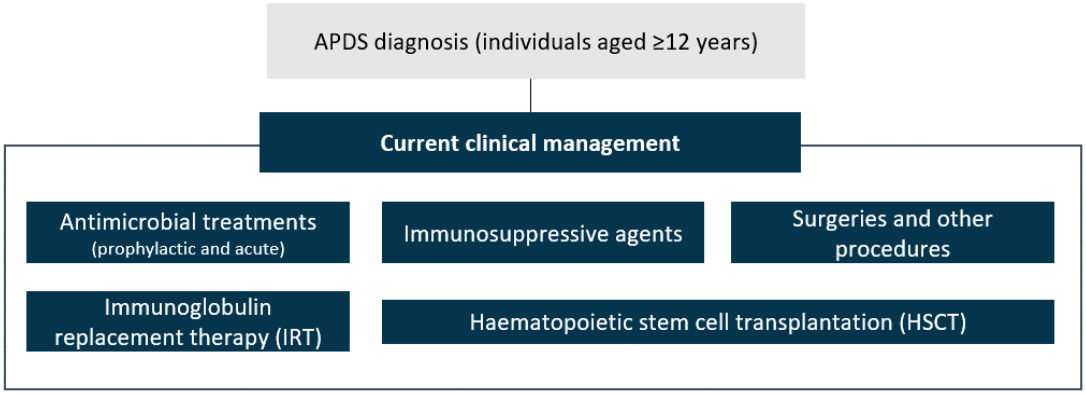
example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for APDS?

There are currently no clinical guidelines for the management and treatment of APDS in England. Different treatments are given to people with APDS based on the manifestations they experience.[71] People with APDS often need several different types of treatments to manage their manifestations.[72] Current treatments that are used include **antimicrobials** (including antibiotics, antiviral and antifungal treatments), antibody replacement therapy (also known as **immunoglobulin replacement therapy** [**IRT**]), **immunosuppressive therapies** (including **steroids**), **haematopoietic stem cell transplantation** (**HSCT**) and surgery or other procedures (such as removal of the **tonsils** [**tonsillectomies**]).[1, 31, 71] The diagram below shows how treatments are used in APDS and are all explained in further detail in the following sections.



Antimicrobials

Antimicrobials include antibiotics, antivirals and antifungals, and are used to treat infections from different outside invaders (bacterial, viral and fungal). Most people with APDS take antimicrobials as a preventative treatment to reduce the risk of infections (particularly individuals with bronchiectasis-associated airway disease).[13, 28, 73-75] If people with APDS develop an infection, they will also be given additional antimicrobials to treat it.[13] Antimicrobials can cause **side effects**, such as diarrhoea, nausea and vomiting.[76] Long-term use of antimicrobials could also lead a person with APDS to suffer from the problems associated with **antimicrobial resistance**.[77] This means that future infections in that person may be harder to treat using antimicrobials.[78, 79] Furthermore, antimicrobial resistance poses a serious threat to human health across the world, and contributes to millions of deaths every year.[77] It is therefore important to minimise the use of antimicrobials, where possible.[77]

Immunoglobulin replacement therapy (IRT)

People with APDS do not develop the normal amount of some types of antibodies. IRT replaces some types of antibodies and can be given via **intravenous infusion** or **subcutaneous infusion**.[13, 44] The effects of IRT are only temporary, regardless of how the infusion is given.

Intravenous infusion occurs in hospital and is when the medicine is given via a drip into a vein. Since the effects of the medicine are only temporary, many people need to receive IRT every two, three or four weeks.[44] This may be very inconvenient for people with APDS and their caregivers as the infusion lasts approximately two to four hours. People may also spend long periods of time travelling to and from the hospital.[44]

IRT can also be given via subcutaneous infusion via an injection into the skin. Subcutaneous injections can be administered on a weekly basis,[80] and can take approximately 2–5 minutes (using a manual syringe) or up to 60 minutes (using a weekly pump).[81]

People may experience side effects after receiving IRT via either route, such as rashes, fever, itching, shivering and headaches.[82] IRT may also lead to more serious side effects, such as kidney damage, increased risk of blood clots and problems with the lungs and heart.[83] Furthermore, IRT is not an option for people with APDS who have a phobia of needles.[82]

Immunosuppressive therapies

Immunosuppressive therapies lower the activity of the immune system, to control autoimmune manifestations. Steroids, rituximab and mTOR inhibitors are all types of immunosuppressive therapies used to treat people with APDS. These treatments may increase the risk of infection.[84] They are also associated with side effects, like gut swelling, weak bones, high blood pressure, fever, chills, rashes and damage to the liver (depending on the treatment).[31, 85-89] In addition, long-term use of steroids may increase the risk of cancer in these individuals.[90]

Surgery

People with APDS often have swollen organs, such as lymph nodes, the spleen, the liver or tonsils. Surgeries may be required to treat this swelling.[9, 31] This can include removing the swollen organ, and/or performing organ transplants. However, surgery is often not effective in people with APDS, and can lead to side effects and increase the risk of infections.[9, 10, 31, 43]

Haematopoietic stem cell transplant (HSCT)

HSCT is also known as a ‘bone marrow transplant’ because it replaces an individual’s bone marrow cells with healthy cells from a donor. HSCT is a high-risk and very invasive procedure. The risks depend on many factors including age. Individuals must undergo complex procedures and treatments to prepare for HSCT.[91-96]

Additionally, the patient needs an appropriately **matched donor** for successful HSCT. This means someone who is genetically closely matched to the recipient, who has healthy bone marrow, and who can donate bone marrow cells. Some people cannot undergo HSCT, as they cannot find an appropriately matched donor.[97, 98]

There is no clear guidance on the use of HSCT for people with APDS in the UK, and long-term data on the outcomes of HSCT for APDS are not yet available. However, in adults with APDS, HSCT is generally used as a final treatment option after severe disease progression and/or irreversible end-organ damage, when other treatments have failed, or when there are concerning risks associated with long-term use of other treatments. For example, HSCT may be performed when an individual has developed lymphoma, or when the treatments are unable to control their manifestations to a tolerable level.[13, 19, 28, 99, 100]

For younger people with APDS, HSCT may be considered as an early treatment (on a case-by-case basis) to prevent future disease progression and/or irreversible end-organ damage. Use of HSCT in childhood also increases the chances of a successful HSCT outcome.[13, 19, 28, 99, 100]

HSCT may lead to serious side effects, such as vomiting, hair loss and organ damage.[101] About 90% of people with APDS experience serious complications from HSCT.[100, 102, 103] HSCT is also not always effective in people with APDS. In about one third of people, their body rejects the transplanted bone marrow cells, and many people with APDS require multiple transplants.[102, 104] Furthermore, approximately 10–20% of people with APDS do not survive beyond two years following HSCT.[13, 103, 105] Evidence shows that survival rates for 158 people with IEIs after HSCT ranges from 54–100%;[100] outcomes after HSCT are generally worse for people with APDS compared to those with other IEIs.[100, 102, 103]

When would leniolisib be given?

People with APDS would take leniolisib continuously as a twice a day oral tablet.[106] Leniolisib can be given after a diagnosis of APDS is reached by a clinical immunologist based on the results of a genetic test.

Leniolisib can be taken instead of, or alongside, existing treatments. A doctor will manage which existing treatments to take alongside leniolisib and when.

For the drug-drug interactions and contraindications for leniolisib, please refer to the label.[107]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

To gain as much input as possible from people living with APDS and their families and caregivers, Pharming have compiled various published patient testimonies and have also conducted several interviews.

APDS from the patient perspective

Living with APDS can lead to feelings of anxiety, stress and loss of hope, and individuals struggle to live a normal life.

"Many of the challenges I have faced [with APDS] are mostly to do with trying to live a normal life – combining school, work and socialising with hospital visits, spending months at a time in hospital and being poked and prodded with needles. APDS has affected me a lot; it still does."[62]
"Growing up I didn't really think I'd make it very far, didn't plan for a lot of things in my future, like going to college because I didn't think I'd have a future to plan for."[108]
"It would be very meaningful, not having to worry about the lumps, not having to worry about those lumps turning into lymphoma, the pain, obviously. Yes, so that would be nice not to have to worry about that."[47]

Cancer (e.g. lymphoma) has a particularly negative impact the quality of life of people with APDS. People with APDS who are diagnosed with cancer face a lot of mental stress and a drop in the quality of their life, feeling anxious and isolated. In addition, regular hospital visits for treatment add extra stress and upset their daily schedules.[47, 48]

Lung disease can also make people with APDS feel tired and less energetic and can cause **sleep apnoea** (when breathing stops and starts during sleep). This makes it hard for people with APDS to take part in their hobbies and do everyday tasks, leading to feelings of frustration.[47, 48] People with APDS have reported that they experience chest pains, difficulty breathing, as well as anxiety about the lung damage that they have experienced.[47, 48]

"…obviously it's the lung damage side the obviously breathing harder especially when it's cold"[48]
"I'm well aware that PI3K effects the structure of my lungs, there's repeating scarring that I can get from my asthma…"[48]

Below are the summarised additional impacts of individual manifestations on patient quality of life that were reported by patients and/or caregivers, families and friends:

- When the body produces too many WBCs, this can lead to swollen and painful lymph nodes all across the body and may impact the individual's ability to sleep, breathe and eat (with gagging and difficulty swallowing reported).[47, 48, 109, 110]
- Gastrointestinal manifestations can lead to disabling and frequent symptoms in people with APDS,[111] with individuals struggling with their diet, maintaining weight, experiencing stomach pains, requiring a gastronomy tube (G-Tube) for nutrition, as well as experiencing chronic diarrhoea. All of these symptoms impact sleep and daily activities, including work.[47, 48, 62, 112]
- In order to avoid catching infections, people with APDS often make lifestyle adjustments such as practicing social distancing, which means they often are unable to socialise, go to school or work, or attend milestone events.[47, 48]

Beyond the individual manifestations, APDS also has a negative impact on energy levels and mental health. People with APDS report feeling "exhausted" and "drained, both mentally and physically", due to various manifestations (and associated symptoms) and frequent hospitalisations. People with APDS have also reported that they have a "constant lack of energy" and "just crushing fatigue", which stops them from carrying out their daily activities. Individuals with APDS also report feeling sad, isolated, anxious and frustrated as a result of living with APDS, as the condition creates difficulties in making friends and maintaining interpersonal relationships.[20, 47, 48, 108]

> *"My mental health has been put to a hard test and, although a private psychological support, I'm going on fighting with permanent anxiety relevant to the fact that my body could let me down at any moment."*[111]

APDS from the caregiver perspective

Due to the severe and complex manifestations they experience, many people with APDS require physical and emotional support from caregivers. The stress of caring for individuals with APDS, in turn, may have a negative impact on the emotional wellbeing of caregivers (for example, there have been reports of depression, anxiety and anger). Caregivers have also reported that their caring responsibilities affect their daily responsibilities. For example, they may have to reduce their working hours to attend hospital appointments and/or manage medical issues.[47]

APDS may also impact wider family life. For example, there may be restrictions on family holidays, due to concerns that certain destinations may have greater risks of infections and due to logistical difficulties, such as working around treatment schedules. Caregivers also report that their caregiving responsibilities negatively impact their relationships with loved ones, due to low moods or lack of time.[47]

> *"It's meant that I've possibly missed some employment advancement opportunities because of my absence, and it also can cause a bit of strife with co-workers who happen to pick up my end of the workload… in my absence."*[111]

"We don't get together with people like we used to, just because either A, it's not exposing her to other stuff, or we're too tired to or she just is not feeling up to it, and so then we cut that out."[111]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

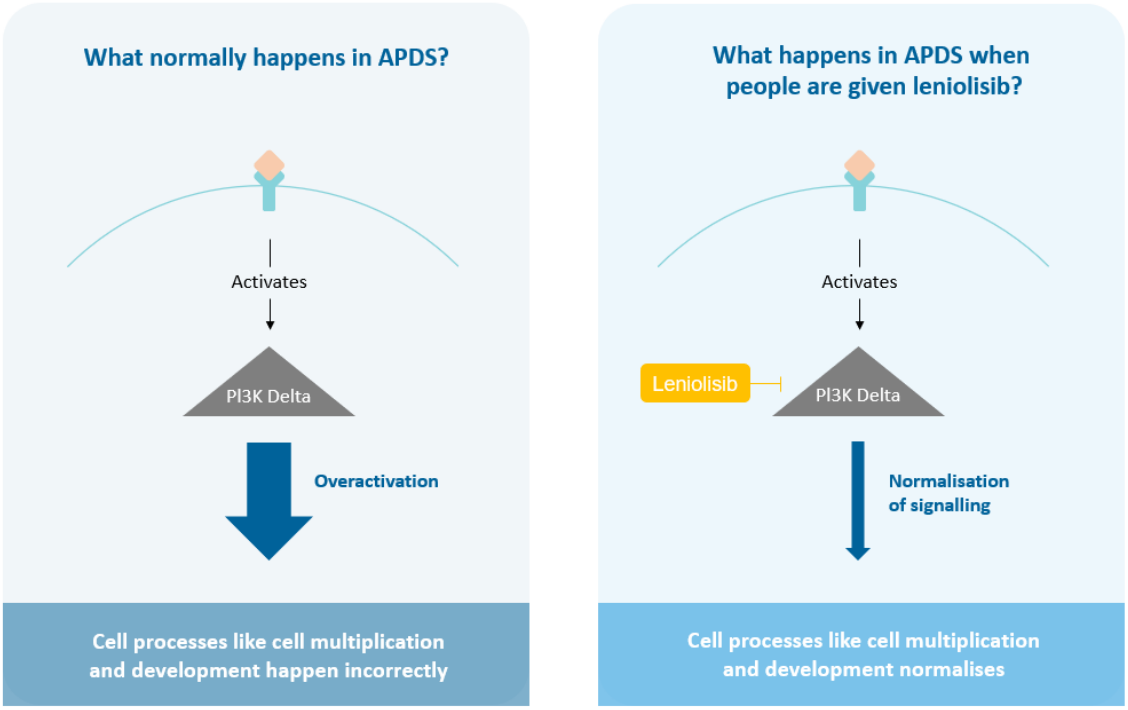
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How does leniolisib work?

As mentioned above, APDS is caused by overactivity of a protein called PI3K delta, which leads to immune dysregulation and immune deficiency (see Section 2a above). Leniolisib is a **PI3K delta inhibitor** that specifically lowers the activity of PI3K delta (i.e. reduces its ability to send signals), which means PI3K delta signalling normalises (see below).[24, 71]



By lowering the activity of PI3K delta in people with APDS, leniolisib normalises the number of WBCs to the levels seen in the general population. This helps to restore the normal functioning of the immune system in people with APDS.[24, 71]

Innovation in patient care

Leniolisib works differently to other treatments for APDS. Leniolisib will be the first **targeted therapy** for APDS in England and Wales. This is because leniolisib selectively targets the overactive PI3K delta protein, which means it treats the underlying cause of APDS, unlike other therapies. For example, antibiotics kill bacteria to treat or reduce the risk of infections, but they do not address the overactive PI3K delta protein.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Leniolisib does not have to be given in combination with any other treatments, although doctors may choose to give leniolisib alongside some existing treatments (see Section 2c).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is leniolisib taken?[106]

A person with APDS must always use this medicine exactly as their doctor has instructed. Leniolisib is to be orally taken (swallowed) in tablet form and can be taken at home.

How much medicine do people with APDS take and when?[106]

A person with APDS should take one tablet containing a total of 70 mg leniolisib, twice a day. Leniolisib tablets should be taken approximately 12 hours apart, with or without food.

If vomiting occurs within one hour after taking leniolisib, another leniolisib tablet should be taken as soon as possible. If vomiting occurs more than one hour after taking leniolisib, the individual should wait until the next tablet is due to be taken.

Taking leniolisib with other medicines[106]

A person with APDS will be advised about taking leniolisib in combination with other medicines by their doctor.

If a person with APDS has been taking some alternative medicines, the individual's doctor will advise how long other medicines should be stopped for before commencing leniolisib.

If a person with APDS takes more leniolisib than they should:[106]

They should contact their doctor or nearest emergency department immediately for advice. The medicine bottle and information leaflet should be kept with them so that the person can easily describe what they have taken.

If a person with APDS forgets to take leniolisib:[106]

If a person with APDS forgets to take a leniolisib tablet by more than 6 hours, they should not take the missed tablet and wait until their next tablet is due to be taken.

When should a person with APDS stop taking leniolisib:[106]

People with APDS should not stop taking this medicine unless advised to by their doctor.

Comparison to existing treatments

Leniolisib can be taken alongside some existing treatments. Leniolisib can reduce or stop the need for some existing treatments, so a doctor will manage which existing treatments to take alongside leniolisib and when.

Leniolisib is taken in a different way to other treatments for APDS. For example:

- Leniolisib is a tablet taken orally.[106] Some other treatments for APDS are given via an injection into the skin or into a vein via a drip (e.g. IRT)[44]
- Leniolisib is taken at home, whereas some other treatments are taken in the hospital (e.g. intravenous infusions of IRT)[44]
- Leniolisib is taken two times a day,[106] whereas other treatments might be taken more often or less often
- Leniolisib should be taken every day until a doctor advises you to stop, whereas other treatments might only be taken for a few weeks at a time (e.g. steroids)

3d) Current clinical trials

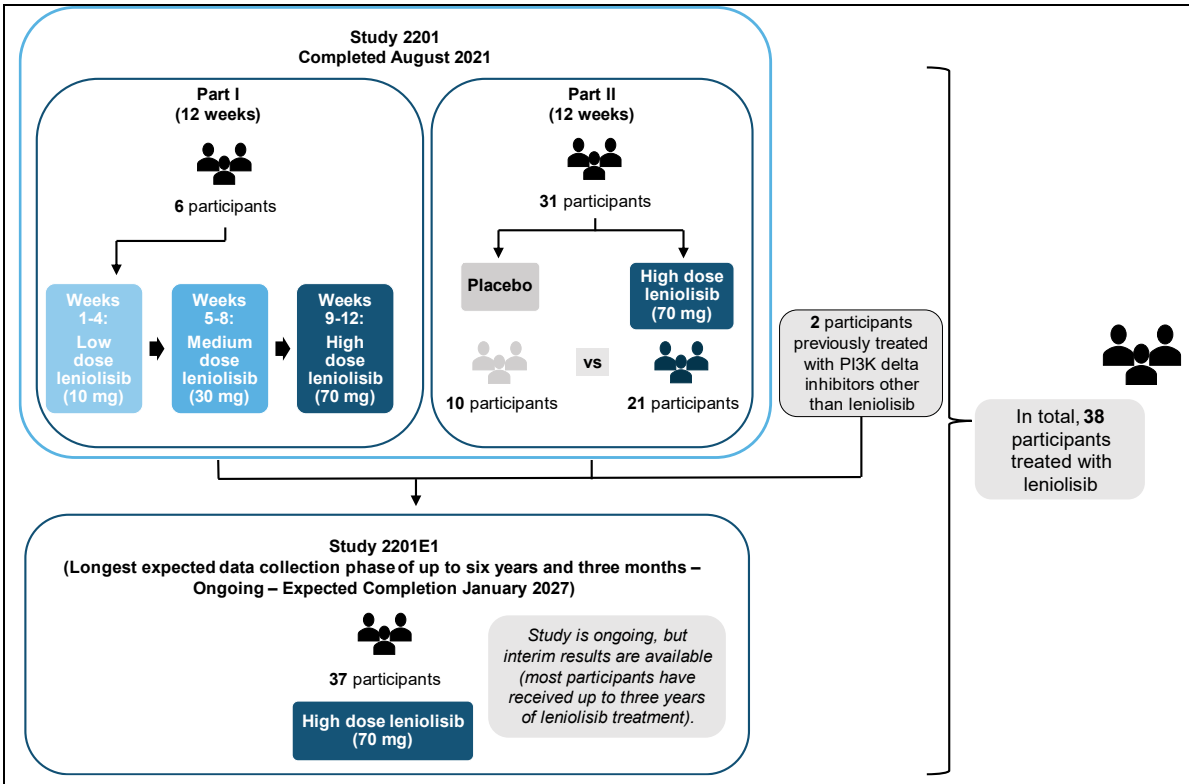
Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of leniolisib in APDS

Three **clinical trials** have been conducted to study leniolisib for the treatment of APDS. A clinical trial is a type of research study that compares the effects of one treatment with another or **placebo**. They are called Study 2201 (Part I and Part II) and Study 2201E1. The trials were conducted globally.[24, 71, 113]

Study 2201 (NCT02435173)[114]	**Part I**	Study 2201 Part I was a **Phase 2 trial**. In this study, researchers focused on how much leniolisib people with APDS should take. They looked at a low dose, a medium dose and a high dose. This helped the researchers to decide which dose to use in Part II of the study. The researchers also used Part I to learn more about the **efficacy** and **safety** profile of leniolisib.[71]
	Part II	Study 2201 Part II was a **Phase 3 trial**. This means researchers looked at how well leniolisib worked to treat APDS (its efficacy) and to understand the safety profile of leniolisib. Participants received either leniolisib or placebo.[113]
Study 2201E1 (NCT02859727)[115]		Study 2201E1 is an **extension study** which is currently ongoing (although people are no longer being recruited for this study). In this study, researchers are looking at the efficacy and safety profile of leniolisib in the longer term. Participants who completed Study 2201 Part I or Study 2201 Part II could enter Study 2201E1.[24, 115]

The trials also looked at the impact of leniolisib on people's quality of life. A summary of the key information about each trial is provided in the figure below.



These studies looked to enrol people with APDS, specifically:[114, 115]

- Both male and female participants aged 12–75 years old
- Participants had to have a minimum body weight of 45 kg
- Participants had to have APDS-specific disease-causing variants, identified by genetic testing
- Participants had to have swollen lymph nodes that could be measured using imaging machines
- Participants had to have a history of common APDS manifestations (e.g. infections)

More information about Study 2201 Part I, Study 2201 Part II and Study 2201E1 can be found here:

- Study 2201 Part I and Part II (NCT02435173)[114]
  - Rao et al., 2017[71]
  - Rao et al., 2023[113]
- Study 2201E1 (NCT02859727)[115]
  - Rao et al., 2023 (interim results)[24]

Expanded Access Programme

Pharming have established a global **Early Access Programme** (EAP), to provide leniolisib to a total of 72 individuals with APDS. A survey of doctors treating patients with leniolisib in the EAP was conducted in October 2023. Results from this survey have been presented throughout **Section 3e.**[116]

Delphi panel

To understand what a meaningful change would be for patients in the clinical trials, a group of experts were asked for their insights. In total, 24 doctors with experience treating

people with APDS or PIDs took part in several rounds of surveys, which is called a Delphi panel.[117]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

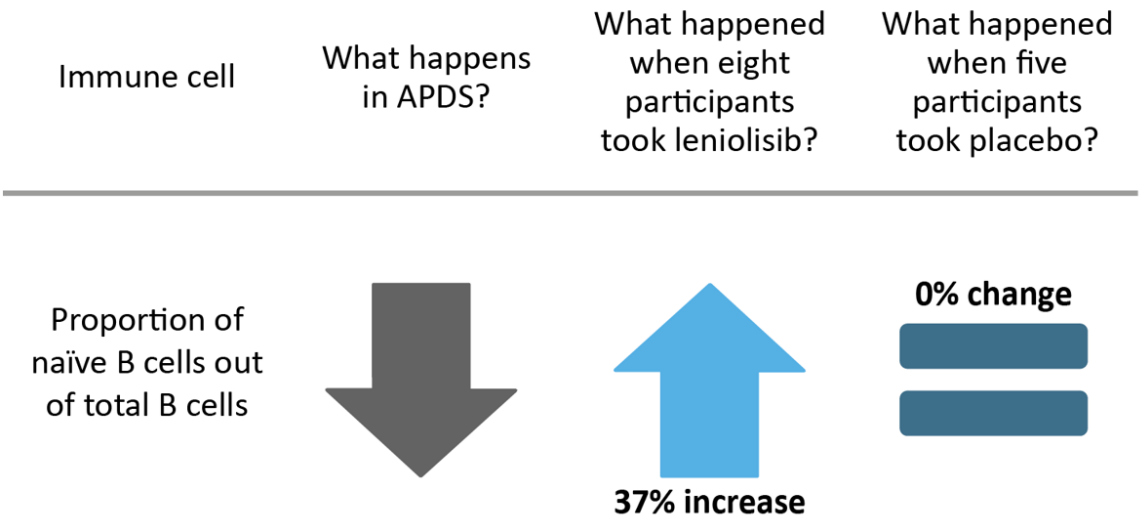
In the clinical trials, Study 2201 (Part I and Part II) and Study 2201E1, the efficacy of leniolisib was measured according to how well it changed certain markers of disease severity, such as the size of participants' lymph nodes or organs (via scans using special imaging machines) and the numbers of different types of WBCs (via blood tests).[24, 71, 113]

For Study 2201 Part I and Study 2201 Part II, efficacy was assessed following 12 weeks of treatment. Study 2201E1 is ongoing, and a set of interim results were made available with some participants receiving six years of leniolisib treatment.[24, 71, 113, 118] The key efficacy and safety results are explained below.

White blood cell and antibody levels

People with APDS have a lower proportion of naïve B cells out of all B cells than people without APDS. This means that their immune system doesn't work as well as in healthy people without APDS.[113] This is described further in **Section 2a** above. To look at the effect of leniolisib treatment on WBCs, researcher looked at blood samples from participants and used special equipment to count the numbers of different WBCs (including naïve B cells).[113]

At the end of Study 2201 Part II, leniolisib was more effective than placebo at increasing the proportion of naïve B cells out of all B cells in participants. The researchers concluded that this was **statistically significant**.[113] Returning towards a normal proportion of naïve B cells may help the immune systems of participants to work more correctly. This will mean that they are better at fighting infections.

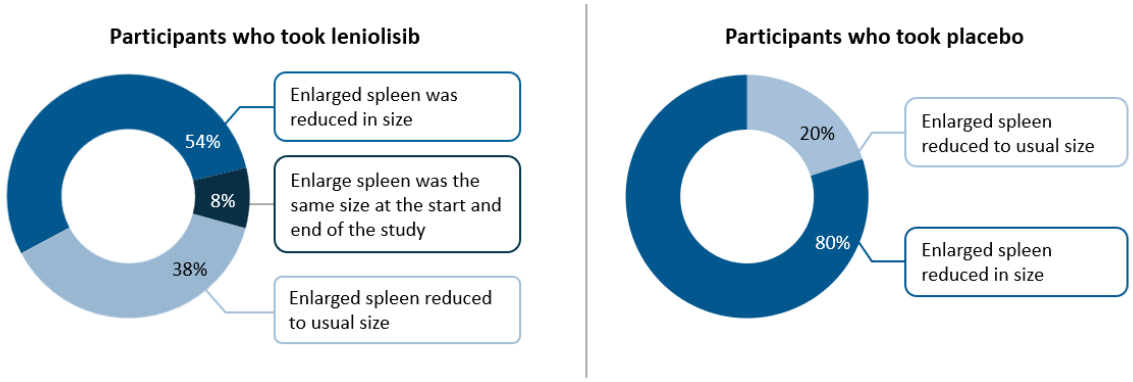


On average, participants' WBCs and the different antibody types reached normal, healthy levels with leniolisib treatment. These improvements lasted through the long-term extension study.[24, 113]

Lymphoproliferation

As discussed in **Section 2a**, people with APDS can experience lymphoproliferation. This can lead to swollen lymph nodes, spleen and/or liver.[51, 52, 54, 109] Researchers took images using imaging machines to measure the size of these lymph nodes and organs in participants. This allowed the researchers to see how much their size had increased.[24, 113]

Researchers compared the size of (up to) six of the participants' most swollen lymph nodes before and after treatment. Leniolisib was more effective than placebo at shrinking the swollen lymph nodes. This indicates immune cells were multiplying less than they were before leniolisib treatment started. These changes were **statistically significant**.[113]



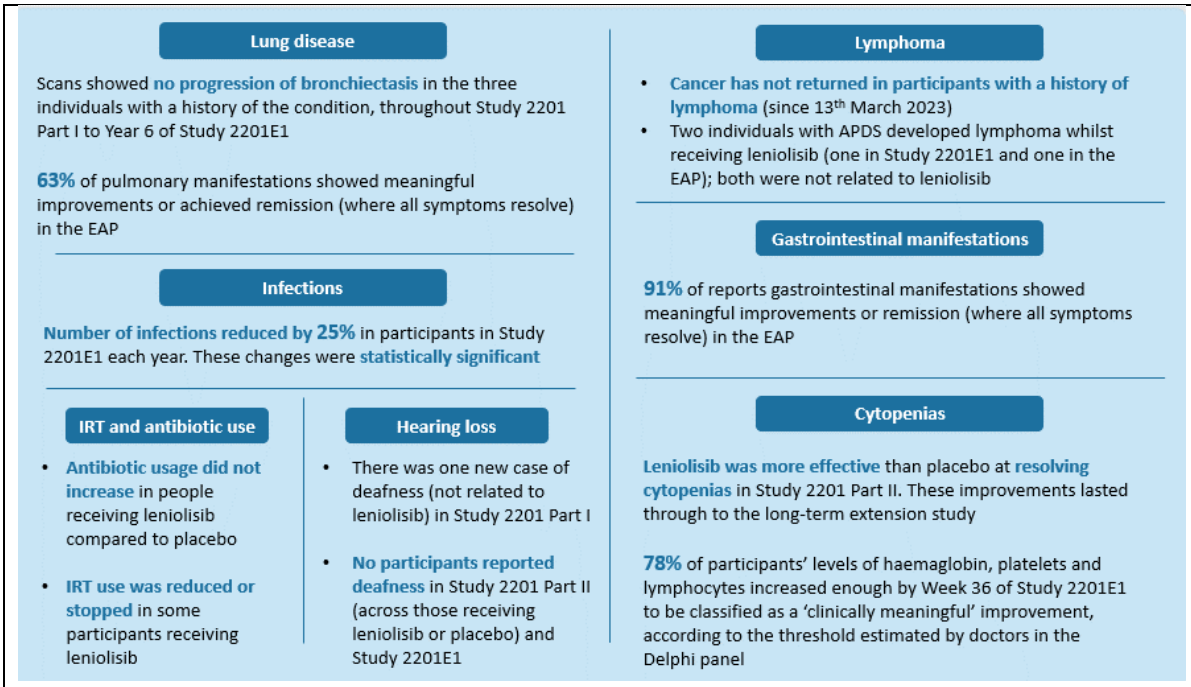
For people who had enlarged spleens; leniolisib was also more effective than placebo at reducing the size and volume of the spleen. These changes were **statistically significant**.[113, 119]

Through to Week 24/36 of Study 2201E1, 96% of participants' lymph nodes and spleens shrunk enough to be classified as a 'clinically meaningful' improvement, according to the threshold decided by doctors in Delphi panel.[117]

These results suggest that leniolisib helped to normalise people's immune systems.

Further measures of immune dysregulation and immune deficiency

Leniolisib treatment was effective across a wide range of measures associated with immune dysregulation and immune deficiency.



Overall, these results indicate that long-term treatment with leniolisib led to improvements in the immune dysregulation and immune deficiency observed in people with APDS.[24, 113, 116, 117]

More **efficacy** results can be found in Document B, Section B.2.6.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of leniolisib

During the clinical trials, participants answered questions about their quality of life and wellbeing. They used two different types of questionnaires: the 36-item Short Form Survey (SF-36) [which measured quality of life] and the Patient Global Assessment scale (PtGA) [which measured wellbeing].[24, 113, 119-121]

The results from these questionnaires showed that:[119-121]

- Before starting leniolisib treatment, the clinical trial participants had a worse quality of life compared with the general population,
- Results for SF-36 and PtGA were relatively similar between participants who took leniolisib or placebo in Study 2201 Part II. Slight improvements in SF-36 and PtGA were seen in participants receiving leniolisib compared with placebo. However, these results were not statistically significant,
- Leniolisib led to some meaningful improvements in physical functioning and general health in the long-term extension study,
- Leniolisib improved the wellbeing of participants in the long-term extension study.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In the clinical trials, leniolisib was generally well **tolerated**.[24, 71, 113] Very common side effects (which affects more than 1 person out of 10) were experienced by people during the clinical trials for leniolisib included sinusitis, headache, tachycardia, diarrhoea, dermatitis atopic, alopecia, back pain, neck pain, fatigue and pyrexia.[106]

Participants receiving leniolisib had fewer serious side effects than those receiving placebo in Study 2201 Part II. Serious side effects included shortness of breath, high blood pressure in the lungs and heart or possible signs of damage to the **pancreas**, **kidney** or **gallbladder**. The researchers concluded that none of the serious side effects were related to leniolisib.[119]

During Study 2201 Part I and Study 2201 Part II, no participants experienced a side effect which led them to stop (discontinue) their treatment. However, approximately three and half months after receiving the final dose of placebo, a participant died due to pulmonary hypertension. This participant did not receive leniolisib.[119, 121]

In Study 2201E1, one participant experienced a serious side effect (a heart attack) and discontinued treatment and died the following day. The researchers concluded that this serious side effect and the participant's death were not related to leniolisib.[120] Additionally, two cases of blood cancer (lymphoma) were reported by individuals with APDS (one in Study 2201E1 and one in the EAP), which led them to discontinue their treatment. The researchers concluded that both cases of blood cancer were not related to leniolisib.[19, 122] Overall, the researchers concluded that no deaths were related to leniolisib treatment.

Managing side effects

If a person taking leniolisib experiences any side effects, they should talk to their doctor or pharmacist. This includes any side effects not listed above.

Side effects can also be reported via the national reporting system on the MHRA website and via safety@pharming.com or +31 71 5247 110.

By reporting side effects, more information can be provided on the safety profile of leniolisib.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of leniolisib to people with APDS include:[24, 71, 113, 116]

- Leniolisib helps to lower PI3K delta activity, indicating that it targets the root cause of the disease. Whilst doing so, leniolisib remains generally well-tolerated.
- Leniolisib brings certain markers of disease severity towards normal levels in participants with APDS. This includes markers of both immune dysregulation and immune deficiency.
- In turn, leniolisib reduces or resolves some of the manifestations experienced by people with APDS, such as infections, cytopenias and gastrointestinal manifestations. This has been seen in the clinical trials and the EAP survey.
- Leniolisib may also prevent the progression of bronchiectasis in individuals with APDS, stopping further disease progression.
- Leniolisib also reduces and can stop the use of some existing therapies (e.g. IRT).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?

- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Some things that people may want to consider before starting treatment include:

- Like all medicines, leniolisib does not work equally as well for everyone with APDS. Some individuals might experience less benefit than others.
- Like all medicines, some individuals may experience side effects while they are taking leniolisib. Side effects are possible regardless of how much an individual benefits from leniolisib (see **Section 3g**).[106]
- Leniolisib must be taken twice a day, every day, until a doctor advises an individual to stop.[106] Treatment is likely to last for an individual's lifetime.
- Leniolisib can be taken orally as a tablet, which may be more convenient for most people compared to other treatments.[106] However, some people find it difficult to swallow tablets.
- Some people may need to keep taking other treatments alongside leniolisib, like antibiotics and IRT.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

A new **health economic model** has been developed to help healthcare administrators get the best value of leniolisib from their limited budgets. Using the health economic model, an analysis was performed to compare the costs and benefits of the new treatment (leniolisib) with **current clinical management** in treating people with APDS.

How the health economic model reflects APDS and current clinical management

In order to assess the **cost-effectiveness** of leniolisib in treating APDS versus current clinical management, a health economic model was developed. The health economic model was made up of three '**health states**', which individuals could move between. These were:

- 'Alive and receiving leniolisib'
- 'Alive and not receiving leniolisib' (i.e. alive and receiving current clinical management)
- 'Death' due to the possibility of death in APDS

To capture the lived experience of people with APDS over an entire lifetime (from the age of 12 years old), the health economic model tracked:

- How people with APDS may experience an increasing number of common manifestations over time, including lymphoproliferation, cytopenia, gastrointestinal manifestations, cancers, infections, hearing loss and lung disease
- How people with APDS may need an increasing number of treatments over time, including IRT, antimicrobials, immunosuppressive therapies, HSCT and surgeries
- The costs to the NHS of treating these manifestations, and of these current clinical management treatment options, and
- The impact that these manifestations and treatments have on the quality of life of individuals with APDS

The proportions of people experiencing different manifestations and using various current clinical management treatments in the health economic model were taken from the European Society for Immunodeficiencies (ESID) registry which includes patients with APDS across Europe, including the UK.[123, 124]

Experienced clinicians and other experts agreed that many aspects of the health economic model reflected the reality of living with APDS.

Modelling to what extent leniolisib influences APDS manifestations and treatment use

Leniolisib was modelled to provide the following benefits compared to current clinical management:

- Reduce the severity of some manifestations, for some people
- Completely alleviate some manifestations, for some people
- Reduce how many new cases of all manifestation occurred
- Reduce the use of current clinical management treatments

The extent to which leniolisib provided these improvements in the health economic model was taken from the results of the clinical trial, EAP and insights from clinicians.

The health economic model assumed that 3.5% of people receiving leniolisib would discontinue leniolisib treatment each year. This number was based on the rate of treatment discontinuation in the clinical trials and EAP. In the health economic model,

once individuals discontinued leniolisib treatment, their manifestation and treatment rates steadily increased to reach the same rates as people with APDS who received current clinical management.

Modelling how much leniolisib improves quality of life

There were no data, suitable for the economic model, on how APDS manifestations and treatments affect the **quality of life** for people with APDS. Therefore, the extent to which each manifestation and treatment affected quality of life in the health economic model was estimated from similar manifestations in other conditions, confirmed by clinicians. Clinicians also completed a survey to estimate quality of life in APDS for the health economic model.

As described above, leniolisib was modelled to provide benefits to individuals' manifestations and treatments compared to current clinical management. By consequence, the impact that these manifestations and treatments had on quality of life was improved with leniolisib treatment (compared to current clinical management), in the health economic model.

Modelling how NHS costs differ with leniolisib

Various NHS costs were included in the model for the treatment of APDS. These costs include:

- The cost of leniolisib itself
- The cost of current clinical management
- The cost of treating APDS manifestations
- The cost of regular doctor/hospital visits for these patients (such as visits to a clinical immunologist)

As described above, leniolisib was modelled to provide benefits to individuals' manifestations and treatments compared to current clinical management. By consequence, the costs of manifestations, treatments and regular doctor/hospital visits were reduced with leniolisib treatment (compared to current clinical management), in the health economic model.

Uncertainty

As APDS is an ultra-rare disease, there was a lack of APDS-specific data to use in the health economic model, which can make the results of the health economic model uncertain. Additionally, the leniolisib clinical trials and EAP had small numbers of participants compared with trials for non-rare diseases,[24, 71, 113, 116] which means there may be uncertainty in the clinical data used in the health economic model. Also, in order to develop the model, some assumptions were made where data were not available. Information on these assumptions can be found in **Document B, Sections B.3.6 and B.3.8.2**.

Variations of inputs in the health economic model were also tested. The results of these tests are explained in **Document B, Section B.3.10.**

Cost effectiveness results

Leniolisib treatment was associated with higher costs, but also higher benefits ('**quality-adjusted life years**' [**QALYs**]) than current clinical management. This resulted in an **incremental cost-effectiveness ratio** (**ICER**) near the threshold that the NHS considers to be cost-effective (£100,000 per QALY gained), according to the company's inputs and assumptions.

Benefits of leniolisib not captured in the economic analysis

The economic model did not capture all the benefits of leniolisib, including:

- Improved productivity, such as increased working hours at work/school, associated with leniolisib treatment[119, 122]
- The positive expected impact of leniolisib treatment on patient caregiver HRQoL (e.g. improved productivity and general wellbeing), given leniolisib treatment can lead to improvement in manifestations in people with APDS[108, 119]
- Treatment with leniolisib may lead to improvement in other manifestations associated with APDS,[125-127] but hasn't been included in the model due to lack of evidence
- Reducing the need for IRT helps the NHS by making it easier to manage supplies. Also, during times when IRT is in short supply, like during the COVID-19 pandemic, having fewer people on IRT can benefit society as a whole[128]
- Reduced numbers of people presenting with antimicrobial-resistant infections,[129-131] reducing the associated costs and burden

Conclusion

The benefits outlined in Section 3h and the company's economic analysis suggest that leniolisib was associated with a greater benefit to health for patients with APDS, and a greater cost to the NHS, compared with current clinical management. This conclusion is based on the assumptions made in the company's health economic model, which will be considered by the NICE committee evaluating leniolisib.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Leniolisib is an innovative treatment which would represent an important advancement in the treatment of APDS

Leniolisib works differently to current clinical management treatments in APDS. Leniolisib will be the first approved **targeted therapy** for APDS in England and Wales. This is because leniolisib selectively targets the overactive PI3K delta protein, which means it treats the underlying cause of APDS, unlike other therapies. A clinical expert also commented that leniolisib is the first drug shown to make the immune system work correctly, for an IEI that arises due to a change in one gene (like APDS).[19]

In 2022, the MHRA awarded leniolisib the Promising Innovative Medicine (PIM) designation for the treatment of APDS. This is a special status granted in the UK that helps new and innovative medicines get to patients quicker. During their review, the MHRA commented that: "Leniolisib is the only disease-modifying therapy for APDS with a currently active clinical development programme. All existing treatments are only symptomatic, treating only a specific element of the condition with the exception of HSCT, which has significant mortality and morbidity associated".[132, 133]

In addition, in support of the rare and debilitating nature of APDS, the absence of satisfactory treatment options, and the significant benefit offered to patients by leniolisib, Orphan Drug Designation has been granted by the European Medicines Agency (EMA) and Food and Drug Administration (FDA).[134, 135]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Currently, there are no formal treatment guidelines for people with APDS in the UK. This means that people with APDS may not receive the best care and are often treated inconsistently and can receive variable combinations of medicines.

Individuals with African descent are often faced with inequalities accessing HSCT due to having the lowest probability of finding an appropriately matched unrelated donor.[97]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on APDS:

- 'APDS and me' provides information on the cause, manifestations and treatments for APDS: https://www.apdsandme.eu/
- IPOPI's PDF provides further information too: https://ipopi.org/wp-content/uploads/2020/06/WEB_APDS.pdf
- Immunodeficiency UK provides more information on APDS in the UK: https://www.immunodeficiencyuk.org/activated-pi3k-delta-syndrome-apds-2/

Further information on the leniolisib clinical trials:

More information about Study 2201 Part I, Study 2201 Part II and Study 2201E1 can be found here:

- Study 2201 Part I and Part II (NCT02435173)[114]
  - Rao et al., 2017[71]
  - Rao et al., 2023[113]
- Study 2201E1 (NCT02859727)[115]
- Rao et al., 2023 (interim results)[24]

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in health technology assessments
- EUPATI guidance on patient involvement in NICE
- EFPIA – Working together with patient groups https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative
- INAHTA
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients.

Advanced lung disease	A subset of **bronchiectasis-associated airway disease** that has a high impact on life expectancy and quality of life.
Anaemia	A condition in which the body does not have enough healthy **red blood cells**. This can cause iron deficiency.
Antibodies	Substances which are part of the immune system that help to fight off anything that it recognises as '**non-self**', such as outside invaders (e.g. bacteria and viruses). They are produced by **B cells**. There are five different types in humans.
Antimicrobials	Medicines used to prevent and treat bacterial, viral and fungal infections. These include antibiotics, antivirals and antifungals.
Antimicrobial resistance	This happens when bacteria, viruses and fungi change over time and no longer respond to **antimicrobials**. This makes infections harder to treat.
Activated phosphoinositide 3-kinase delta syndrome (APDS)	An ultra-rare **genetic condition** which stops the immune system from working properly. For more information about APDS, see **Section 2a**.
Autoimmunity	This refers to when the **immune system** mistakenly attacks the body's own healthy **tissues** and organs.
B cells	A type of **white blood cell** in the immune system that help to fight off anything that it recognises as '**non-self**', such as outside invaders (e.g. bacteria and viruses). B cells are key for producing **antibodies**.

Bronchiectasis-associated airway disease	Problems that occur when a person's airways get damaged. This causes lots of mucus, coughing, coughing up blood, wheezing and other breathing problems.
Cancer	When abnormal cells divide in an uncontrolled way.
Clinical immunologist	A doctor who specialises in diagnosing and treating people with immune conditions.
Clinical trial/clinical study	A type of research study that investigates how compares the effects of one treatment with another. It may involve patients, healthy people, or both.
Colon	The longest part of the large intestine.
Cost-effectiveness	A measure of producing good results without costing a lot of money.
Current clinical management	The treatments and care currently provided to people in NHS clinical practice.
Cytopenia	A lower-than-normal number of any type of blood cell. For example, reduced red blood cells leads to a condition called **anaemia**.
Developmental delay	Children taking longer to reach developmental milestones than children in the **general population**.
Disease-causing gene variant	A change in the DNA sequence within an individual.
Disease progression	The worsening of a disease over time.

DNA	The molecules inside cells that carry genetic information and pass it from one generation to the next.
Early access programme	Alternative route for patients diagnosed with a serious and/or life-threatening disease or condition to receive a pre-licenced therapy outside of a clinical trial.
Efficacy and effectiveness	Efficacy is the ability of a medicine to produce the expected effect under highly controlled conditions (e.g. a **clinical trial**). Effectiveness is the ability of a medicine to produce the desired effect in practice.
Extension study	This type of **clinical trial** tests the long-term **efficacy** and **safety** of a drug.
Gallbladder	Organ located under the liver that stores and releases bile, a fluid that the liver produces to help digestion of food.
Gastrointestinal	Relating to the stomach and intestines.
Gene	A short section of **DNA**. Some genes act as instructions to make proteins, other genes do not.
General population	The entire population of individuals without reference to any specific characteristics (i.e. for this appraisal, people without APDS).
Genetic condition	A type of disease caused by a **disease-causing variant** in an individual's **DNA**.
Genetic test	A genetic test involves taking a sample of saliva or blood. It looks for a disease-causing variant(s).

Haematopoietic stem cell transplantation	A procedure that replaces an individual's bone marrow cells with healthy cells.
Health economic model	A way to predict the costs and effects of a technology over time.
Health state	A description of someone's health.
Health state transition model	An economic model to understand the progression of a person's **health state** over time.
Hepatomegaly	A condition where the **liver** swells beyond its normal size. Also known as enlarged liver.
Immune deficiency	When the **immune system** no longer works correctly, and the body is unable to fight anything that it recognises as '**non-self**', such as outside invaders (e.g. bacteria and viruses) and abnormally growing and/or infected cells. This means that the person may be more likely to get infections than those in the **general population**.
Immune dysregulation	When the **immune system** no longer works correctly. This may cause the immune system to mistakenly attack the body's own healthy **tissues** and organs.
Immune system	The body's defence against anything that it recognises as '**non-self**', such as outside invaders (e.g. bacteria and viruses) and abnormally growing and/or infected cells. It is made up of cells (like **white blood cells**), **tissues** and organs (like **lymph nodes**).
Immunoglobulin replacement therapy (IRT)	A treatment which replaces certain types of **antibodies** when they are low. The antibodies will help the body to fight against anything that it recognises as '**non-self**',

	such as outside invaders (e.g. bacteria and viruses) and abnormally growing and/or infected cells.
Immunosuppressive therapy	A treatment which makes the **immune system** less active. It is used to treat **immune dysregulation**.
Inborn error of immunity (IEI)	A group of diseases in which people's immune systems do not work correctly.
Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio (ICER), is a number which represents the value for money to the NHS of a new technology. It is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest. In other words, how much more or less a new treatment costs the NHS compared with existing treatment, relative to how much more or less effective it is.
Inflammation	The body's response to an illness, injury or something that is '**non-self**' and doesn't belong in the body.
Intravenous infusion	Giving a medicine via a drip into a vein.
Kidneys	A pair of organs that filter the blood and help the body pass waste as urine.
Liver	The liver is a large organ that processes the breakdown of cells and chemicals absorbed from the stomach. It also produces many essential chemicals such as hormones.
Lymph nodes	In the **general population**, lymph nodes are small, bean-shaped organs in which **white blood cells** cluster to filter out anything '**non-self**' from the body. They also house white blood cells to help fight

	infections and are found all around the body. They are a type of gland and are part of the **immune system**.
Lymphadenopathy	When the **lymph nodes** get bigger because the body makes too many of a certain type of **white blood cell.**
Lymphoma	A type of blood **cancer** that originates within some types of **white blood cells**.
Lymphoproliferation	When the body produces too many of a certain type of **white blood cell**.
Manifestation	The symptoms which are seen as a result of an underlying disease.
Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to people in a particular country.
Matched donor	The donor needs to have stem cells that match person receiving the donation.
Medicines and Healthcare products Regulatory Agency (MHRA)	The **regulatory body** that grants **marketing authorisation** to medicines throughout the United Kingdom.
Naïve B cells	A type of white blood cell that has not been activated by anything ‘non-self’ in the body before.
Non-self	Outside invaders (e.g. bacteria and viruses) or cells that are recognised by the body as its own healthy cells (e.g. abnormally growing/infected cells). A healthy person will initiate an immune response against any non-self-substance.

Pancreas	A gland that produces and releases proteins into the small intestine to help with digestion.
Phase 2 clinical trial	This type of **clinical trial** mainly looks to learn about the best dose and **safety** profile of a new treatment. It may also look at how well the treatment works.
Phase 3 clinical trial	This type of **clinical trial** mainly tests how well a new treatment works (its **efficacy**), as well as its **safety**.
Phosphoinositide 3-kinase (PI3K) delta	A protein that primarily controls how **white blood cells** develop and mature.
PI3K delta inhibitor	A type of **targeted therapy** that lowers the activity of a protein called PI3K delta inside cells.
Placebo	A treatment that appears identical to the treatment of interest, but has no active ingredients and thus no therapeutic benefit. In **clinical trials**, the new treatment is sometimes compared against placebo.
Primary immunodeficiencies (PIDs)	A group of diseases in which people's immune systems do not work correctly.
Protein	Structures inside all cells of the body, that are important for many activities including growth and repair.
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for an individual following a particular treatment or intervention and

	weighting each year with a quality-of-life score (on a 0 to 1 scale).
Quality of life	In the context of health, this refers to the impact of a disease or treatment on an individual's functioning and wellbeing.
Red blood cells	Cells in the blood which contain iron and carry oxygen around the body.
Regulatory agency/body	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
Safety	Assessing whether a treatment is safe to use.
Side effect	An unexpected and unwanted medical problem that arises during treatment. May also be referred to as an adverse event. Side effects may be mild, moderate or severe.
Sinuses	Spaces inside the head that are connected to the back of the nose.
Sleep apnoea	When a person's breathing stops and starts during sleep.
Spleen	An organ above the stomach that removes old, damaged blood cells and helps to fight infections in the blood.
Splenomegaly	A condition where the **spleen** swells beyond its normal size. Also known as an enlarged spleen.
Statistically significant	When it is very likely that the difference in results is because of the effect of the treatment, and not by chance. Statistical

	significance is based on calculations done by researchers.
Steroid	A type of **immunosuppressive therapy** which makes the **immune system** less active.
Subcutaneous infusion	Giving a medicine via an injection into the skin.
Symptom	A feature or sign which is noted by the individual, that indicates an underlying disease.
Targeted therapy	A type of treatment that targets a specific part of how a disease develops.
Tissues	A group of different cells attached together. Tissues are the building blocks for organs.
Tolerated	The ability of a person to take a medicine without feeling too uncomfortable or needing to stop because of severe or unbearable **side effects**.
Tonsillectomy	A surgery to remove the **tonsils**.
Tonsils	Small **lymph nodes** in the back of the throat to help filter substances entering the body that may cause infection.
White blood cells	These are immune cells in the body that fight against anything that it recognises as '**non-self**', such as outside invaders (e.g. bacteria and viruses) and abnormally growing and/or infected cells.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Clarification questions

July 2024

File name	Version	Contains confidential information	Date
ID6130_Leniolisib Clarification Questions_08July2024_Redacted	V1.1	Yes	08 July 2024

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Decision Problem

A1. A weight restriction has been added to the eligible population; this aligns with the proposed marketing indication being considered by the Medicines and Healthcare Products Regulatory Agency (MHRA) but is a deviation from the final scope issued by NICE. After reviewing the UK-WHO growth charts, it seems possible that a sizeable portion of adolescents or teenagers will be ineligible for leniolisib. Could you please provide further background on the decision to apply a weight restriction?

The Medicines and Healthcare products Regulatory Agency (MHRA) is currently reviewing the marketing authorisation application for leniolisib through the International Recognition Procedure (IRP) Route B, with the US Food and Drug Administration (FDA) specified as the Reference Regulator. The NICE scoping meeting was held in January 2023, before leniolisib was approved by the FDA with a recommended dosage for adults and adolescents [redacted], hence the deviation from scope. Currently, there is no dose recommendation for individuals [redacted].

This [redacted] is in place as participants in the pivotal Study 2201 must have had a [redacted] for enrollment; the [redacted] was selected due to oral drug clearance modelling, and its safety and efficacy was established in Study 2201 Part I.[1, 2]

Pharmacokinetic data will be collected from the two ongoing paediatric clinical studies of lower doses of leniolisib (NCT05438407 and NCT05693129 [which includes a site in the UK]), which include doses of leniolisib starting from 10 mg bid.[3, 4] These trials will support future line extension of the marketing authorisation for individuals with APDS aged 1 and above, and will include dose recommendations based on [redacted].

Currently, leniolisib doses below 70 mg bid are being provided via compassionate use for people who are not eligible for a clinical trial.[5]

A2. Could you please clarify the clinical care pathways for adolescents and young people compared to adults and comment on any anticipated differences?

Specialist immunology services are delivered by paediatric immunology departments for individuals with APDS ≤18 years of age,[5] and by adult immunology departments for individuals with APDS aged ≥18 years.[6, 7] Delays in referral to immunology services results in some individuals not receiving a diagnosis of APDS until they are an adolescent or adult.[5] In general, the clinical care pathways for adolescents and young people are similar to adults, with the exception of the role of HSCT.

APDS will be managed as a dynamic condition for individuals of **all ages**. Current clinical management in the UK is limited to supportive care, and polypharmacy approaches are required to attempt to manage the multiple manifestations and symptoms of APDS.[2, 6, 8-12] Treatments for immune dysregulation are immunosuppressive and therefore exacerbate immune deficiency in individuals with APDS, leading to cyclical polypharmacy approaches in an attempt to find a balance.[2, 9, 13] The composition of the polypharmacy regimen depends on the dominant manifestations and the individual's immunophenotype. Over time, the treatment approach often evolves as frequent infections, cytopenias, and lymphoproliferative disease must be managed alongside worsening chronic manifestations such as bronchiectasis.[10, 14]

Since no available treatments directly target PI3Kδ, drug toxicities, off-target effects, or inadequate control of APDS may necessitate considering the risks associated with HSCT.[5] For example, due to concerns regarding the long-term use of some treatment options, such as mTOR inhibitors, children and young adolescents requiring these medicines for two years or more will usually be referred to Newcastle or Great Ormand Street Hospital for consideration to undergo HSCT.[5, 6, 9, 15, 16] Young patients may be considered for HSCT, but for older patients who have accumulated more complexities of disease, HSCT is more sparingly undertaken due to recognition that a good outcome is less likely.[5] This highlights the need for a targeted treatment option.

The tendency to attempt a HSCT-sparing approach may be reflected by the median ages at which HSCTs are performed for individuals with APDS in the UKPID registry, according to an interim analysis (data cut-off [DCO]: March 2024:[17]

- For individuals who underwent HSCT at 12 years of age or above, the median age at HSCT is [redacted] years (interquartile range [IQR]: [redacted] years), and the median time from diagnosis of APDS to HSCT is [redacted] years (IQR: [redacted]).
- In comparison, for individuals undergoing HSCT before the age of 12, the median time from diagnosis of APDS to HSCT is [redacted] years (IQR: [redacted]).

In summary, the clinical care pathways for adolescents and young people are similar to adults, with the exception of HSCT. However, **all individuals of any age** require dynamic disease management for APDS, relying on supportive care and polypharmacy approaches based on individual's dominant manifestations, symptoms and immunophenotype.

A3. The EAG understands the risks associated with HSCT increases with age and are more apparent in adults. Do you expect leniolisib to be used as a bridging therapy for HSCT in adolescents and teenagers?

Across the clinical trials and EAP, including more than 100 individuals with over 236 patient-years of leniolisib treatment,[5] leniolisib has predominantly **not** been intended for use as a bridging therapy for HSCT:

- One case has been documented in which leniolisib was intended to be used as a bridging therapy; in this instance, the patient's HSCT has been repeatedly delayed given the benefits that the patient has experienced since initiating leniolisib.[5]
- Another patient is known to have discontinued leniolisib to undergo HSCT; however, the use of leniolisib as a bridging treatment for HSCT was not the original intention.[5]

Whilst an expert multi-disciplinary team may consider HSCT as a treatment option for adolescents with APDS in order to prevent future APDS-related complications and increase the chance of successful outcomes, not all adolescents with APDS are suitable candidates for HSCT.[5, 6, 9, 15, 16] Access to HSCT in both adolescents and adults is limited by:

- A lack of availability of appropriately matched donors,[16, 18, 19] and
- Other factors such as pre-existing infections and non-infectious co-morbidities or older age may increase the risk of transplant-related mortality. Performing HSCT prior to development of end-organ damage, significant autoimmunity, chronic infection or malignancy may result in less HSCT-related complications.[20]

Despite judicious use and expertly-led clinical management, HSCT carries a two-year mortality risk of 10–20% in people with APDS (across all age groups) and is associated with significant morbidity risks,[9, 21-23] with 62% of transplants resulting in a patient alive and well with phenotype reversal.[22] Due to its association with life-threatening complications and morbidities. HSCT is performed sparingly in individuals aged 12 years and older in the UK.[5, 24-26] According to the last interim analysis of the UKPID registry, the median age of HSCT in the UK is [redacted] years (IQR: [redacted]).[17] As such, the company does not anticipate that leniolisib will primarily be used as a bridging therapy for HSCT in adolescents with APDS in the UK.

The decision to use leniolisib as a bridging therapy for HSCT in adolescents will lie with the physicians responsible for managing APDS patients; they must evaluate the risks and benefits of different treatments, and ensure their patients provide ongoing consent. Based on robust clinical evidence across both adult and adolescent individuals with APDS presented in Document B, Section B.2, it is expected that leniolisib will be prescribed following diagnosis for the treatment of individuals with APDS aged 12 years or older [redacted], regardless of the future potential need for HSCT.

A4. Could you please clarify what outcome measures relating to lung function have been provided in the company submission (CS)? If this is a deviation from the final scope issued by NICE please provide a rationale.

The CS includes the only available evidence on lung function with leniolisib treatment in APDS. In addition, the CS provides evidence on the impact of leniolisib more broadly on bronchiectasis-associated airway disease as well as advanced lung disease,[27-31] which is a subset of

bronchiectasis-associated airway disease with substantial impact on mortality and/or HRQoL.[5] This includes the following evidence:

- Lung function measured using % predicted FEV1, spirometry FVC and SpO_2, from the case report of an individual in Australia treatment in the Early Access Programme (EAP) [Document B, Section B.2.6.4]; this is the only available evidence strictly on lung function with leniolisib treatment in APDS.[27, 28]
- Qualitative assessment of lung symptoms from physicians treating 30 individuals in the EAP (Document B, Section B.2.6.4).[29]
- As part of a case study, the long-term effects of leniolisib on bronchiectasis were analysed by retrospectively evaluating CT images for six participants who received leniolisib for six years in the clinical trials.[30, 31]
- Further data has become available since the CS; lung imaging was retrospectively analysed for all 14 participants in Study 2201 with CT images at screening, 12 weeks, and Day 168 or 252 of Study 2201E1 (see below).[30]

In addition to the evidence presented in the CS, a recent post hoc analysis of Study 2201 and Study 2201E1 investigated the effect of leniolisib on bronchiectasis. In this analysis, 14/37 participants were included (three participants from Study 2201 Part I and 11 participants [seven leniolisib versus four placebo] from Study 2201 Part II); participants were included in this analysis if they had evaluable CT scans at screening, 12 weeks, and Day 168 or 252 of Study 2201E1. The median (min–max) duration between the first and last CT scans was 341 (250–721) days; median (min–max) leniolisib exposure for these participants was 253 (161–342) days. At screening, 57% of participants (8/14) showed radiological evidence of bronchiectasis. In line with the improvements in infection rates and immune dysregulation measures, there was no evidence of development or progression of bronchiectasis between screening and extension Day 168/252 of Study 2201E1. Two patients (randomised to leniolisib during Study 2201 Part II) showed slight improvements in lingular bronchi. This represents further evidence for the beneficial impact of leniolisib on lung disease and therefore functioning in individuals with APDS.[30]

To conclude, evidence relating to the impact of leniolisib on lung disease, including lung function, was presented in the CS (Document B, Section B.2.6.4), in order to ensure that all evidence relevant to the final scope issued by NICE was provided for the EAG's and Committee's consideration.

A5. Could you please clarify what outcome measures relating to liver volume size have been provided in the CS? If this is a deviation from the final scope issued by NICE please provide a rationale.

The outcome measures and results relating to liver volume size are available in the clinical study reports (CSRs) for Study 2201 (Part I and Part II) and Study 2201E1, and have been presented below to fully address the final scope issued by NICE.[2, 8, 32, 33]

In Study 2201 Part II, changes in 3D volume and bi-dimensional size of the liver were assessed as an exploratory endpoint.[8, 33, 34] Effects on liver size were not included as primary or secondary endpoints as they were not expected to provide meaningful insights regarding the impact of leniolisib, for the following reasons. Firstly, in APDS, it is less common for lymphoproliferation to occur in the liver; lymphoproliferative changes are most commonly seen in the lymph nodes and spleen.[35] In Study 2201, there was a history of hepatomegaly in only two participants in Study 2201 Part I (33%) and five participants in Study 2201 Part II (16%) at Baseline. Secondly, with hepatotoxicities observed in individuals treated with PI3K inhibitors for oncology, and various other factors that can impact liver volume outside of lymphoproliferation, a number of variables had the potential to confound treatment effect as measured through liver volume size (although it

is worth noting that both Study 2201 and Study 2201E1 included liver safety monitoring, and no liver toxicities were observed through six years of treatment).[33, 34, 36]

In Study 2201 Part II, reductions from Baseline in liver size were reported with leniolisib treatment at Week 12, as shown in Table 1. In comparison, increases from Baseline in liver bi-dimensional size were seen in the placebo group. Similar reductions were seen for liver organ volume with leniolisib versus placebo.[8, 36]

Table 1. Liver volume and size changes at Week 12 (Study 2201 Part II; PD analysis set)

Parameter	Mean % CfB at D85 in leniolisib 70 mg bid group (SD) n=19	Mean % CfB at D85 in placebo group (SD) n=8
Liver organ volume (mm^3)	−5.58 (9.86)	−6.29 (19.68)
Liver bi-dimensional size (mm^2)	−4.36 (9.96)	+7.22 (15.01)

Abbreviations: bid: Bis In Die (twice daily); CfB: change from baseline; PD: pharmacodynamics; SD: standard deviation.
Source: Study 2201 Part II CSR Version 2.0, Novartis 2022 (Table 14.2-2.7.1b).[36]

Supplementary analyses of Study 2201 Part II demonstrated a statistically significant reduction with leniolisib compared with placebo in liver bi-dimensional size (p=0.0361).[37] The reductions in liver bi-dimensional size seen over 12 weeks of leniolisib treatment were sustained in the long-term extension study. Please see the Section 11.1.2.4 of the CSR for Study 2201E1 for further detail.[33]

Clinical effectiveness evidence

A6. Priority Question: Please complete the following table to clarify which data sources have been used to derive data for the outcomes listed in the first column. Please detail in the relevant box the corresponding sections of the company submission where the outcome data are presented and whether this is primary or supplementary data. Please justify if data for any of these outcomes have been omitted from the CS.

The company has completed Table 2 to clarify which data sources have been used to derive the clinical data presented in the CS for the outcomes/endpoints listed in the first column. The company has removed the row for 'lymphoproliferation' from the table provided by the EAG, as lymphoproliferation is a broader term relating to lymphadenopathy, splenomegaly and hepatomegaly, which are all outcomes included individually within the CS (see table below). The impact of leniolisib on lymphadenopathy was primarily measured by the reduction in index lesion size (an endpoint related to lymphoproliferation), defined as the change from baseline in index lesions (nodal) according to Cheson criteria, in line with the final scope issued by NICE.[2, 8, 32, 37, 38]

Primary data sources for each outcome are marked in **bold** in Table 2. The company systematically included data from all three clinical trials in the submission for all outcomes, where possible. Outcomes not pre-specified in the leniolisib clinical trials, additional data from the Early Access Programme (EAP) and other real-world evidence were also incorporated to provide a comprehensive evidence base for the efficacy of leniolisib in individuals with APDS.

Table 2. Location of evidence from various data sources for the outcomes/endpoints included in the CS

Outcomes/Endpoints	Data source							
	2201 Part I[2, 34]	**2201 Part II**[8, 36]	**2201E1**[33]	**ESID registry (*externally controlled mtahced comparison*)**[39]	**Delphi responder analyses**[a, 40, 41]	**Expert Elicitation**[6]	**Early Access Programme (EAP)**[29]	**RWE studies identified in SLR and updates** (citations individually included below)
Immunophenotype measures								
Normalisation of B cell counts	B.2.6.1 and Appendix N.2.1	**B.2.6.1** and Appendix N.2.1	**B.2.6.1** and Appendix N.2.1		**B.2.6.1**			
Normalisation of T cell counts	Appendix N.2.1	**B.2.6.1** and Appendix N.2.1	**B.2.6.1** and Appendix N.2.1					
Immunoglobulin levels	Appendix N.2.2	**B.2.6.1** and Appendix N.2.1	**B.2.6.1** and Appendix N.2.1	B.2.6.1 and Appendix N.2.2				
Cytokine levels		Appendix N.2.1						
Chemokine levels		Appendix N.2.1						
Immune dysregulation measures								
Lymphadenopathy (as a measure of lymphoproliferation)		**B.2.6.2**	**B.2.6.2**		**B.2.6.2**	B.2.6.2		
Splenomegaly		**B.2.6.2**	**B.2.6.2**		**B.2.6.2**	B.2.6.2		

Outcomes/Endpoints	Data source							
	2201 Part I[2, 34]	**2201 Part II**[8, 36]	**2201E1**[33]	**ESID registry (*externally controlled mtahced comparison*)**[39]	**Delphi responder analyses**[a, 40, 41]	**Expert Elicitation**[6]	**Early Access Programme (EAP)**[29]	**RWE studies identified in SLR and updates** (citations individually included below)
Hepatomegaly[b]	See Clarification Question A.5							
Cytopenias		**B.2.6.2**	**B.2.6.2**		**B.2.6.2**			
Gastrointestinal manifestations		**B.2.6.2 (case study)**[a]					**B.2.6.2 and B.2.6.8**	
Immune deficiency measures								
Infections	**B.2.6.3**	**B.2.6.3**	**B.2.6.3**	Appendix N.2.2			**B.2.6.8**	**B.2.6.8**[42]
Use of IRT	**B.2.6.3**	**B.2.6.3**	**B.2.6.3**					
Antibiotics	**B.2.6.3**	**B.2.6.3**	**B.2.6.3**					
Hearing loss		**B.2.6.3**	**B.2.6.3**			B.2.6.3		
Lung function		**B.2.6.4 (case study)**[a,30, 31]	**B.2.6.4**			B.2.6.4	**B.2.6.4 and B.2.6.8**	**B.2.6.4**[27, 28]
Fatigue	B.2.6.5	**B.2.6.5**	**B.2.6.5**				**B.2.6.5 and B.2.6.8**	**B.2.6.5**[43]
Disease severity and HRQoL	B.2.6.7	**B.2.6.7**	**B.2.6.7**				**B.2.6.7 and B.2.6.8**	**B.2.6.7**[43]
Adverse and serious effects of treatment	**B.2.10**	**B.2.10**	**B.2.10**					

Outcomes/Endpoints	Data source							
	2201 Part I[2, 34]	**2201 Part II**[8, 36]	**2201E1**[33]	**ESID registry (*externally controlled mtahced comparison*)**[39]	**Delphi responder analyses**[a], [40, 41]	**Expert Elicitation**[6]	**Early Access Programme (EAP)**[29]	**RWE studies identified in SLR and updates** (citations individually included below)
Malignancy and mortality	**B.2.6.6**	**B.2.6.6**	**B.2.6.6**			B.2.6.6	B.2.6.6 and B.2.6.8	

Footnotes: [a]Of note, this evidence has been derived from the leniolisib clinical trials. [b]The outcome measures and results relating to liver volume size are available in the CSRs for Study 2201 (Part I and Part II) and Study 2201E1, and have been presented in clarification question A.5.[2, 8, 32, 33]

Surrogate co-primary outcomes

A7. Please provide further justification, and supportive evidence, on the validity of the co-primary endpoints used in 2201 part II as surrogates for longer term clinical outcomes. Please indicate if both endpoints (lymphadenopathy and Immunophenotype (B-cell normalisation)) have been successfully used in other analogous conditions such as other primary immunodeficiency disorders.

The co-primary endpoints measure hallmark manifestations of APDS. Clinicians and regulators in the US and Europe have recognised these endpoints as clinically meaningful, both as direct measures of disease activity that guide treatment decision-making, are linked to long-term outcomes, and are relevant for patients.

In APDS, the hyperactivity of the PI3Kδ signalling pathway has multiple detrimental consequences, including the abnormal development and maturation of immune cells (e.g. B and T cells), causing defects in humoral and cell-mediated immunity.[9, 44-46] APDS is characterised by a combination of both immune deficiency (which can lead to severe, recurrent and/or persistent infections e.g. respiratory tract infections) and immune dysregulation, with damage accumulating over time (e.g. damage within the lung predisposes individuals to end-organ damage such as bronchiectasis).[6, 9, 10, 35, 45] Lymphoproliferation is a key feature of APDS, which most commonly manifests as lymphadenopathy with risk of gut and bronchial obstruction, significant pain and impaired mobility (e.g., neck mobility). Lymphoproliferation can also result in nodular lymphoid hyperplasia (NLH), causing severe organ dysfunction where NLH occurs (e.g., colitis in the gut).[10, 47-49] Other important sequalae of APDS are autoimmune complications and malignancy, most often lymphomas.[10]

Therefore, considering the above, the goals of treating APDS are both normalisation of the immune system and reduction of lymphoproliferation; clinicians currently look to manage lymphoproliferation with mostly off-label immunosuppressive treatments (e.g., sirolimus, rituximab, high dose corticosteroids) which are associated with significant toxicity and disease burden.[13, 50-53]

According to regulatory bodies, the clinical meaningfulness of measuring the percentage of naïve B cells and lymphadenopathy in individuals with APDS is clear:

- The US FDA assessment report states that **lymphadenopathy** "reflects clinical course as it is a direct consequence of the underlying immune dysregulation, is a hallmark of the disease, and if left uncorrected, can lead to obstruction or lymphoma. Reduction in lymphadenopathy, which is not expected to occur spontaneously without intervention, would imply correction of the underlying immune dysregulation."[54] Regarding **naïve B cells**, the FDA stated "correction of immunophenotype with regard to B cell subsets, as measured by change from baseline in percentage of naïve B cells out of total B cells at day 85, is considered both a clinically meaningful measure of response to leniolisib as well as a direct measure of effect of leniolisib".[54]
- The EMA has also stated that "[redacted]," based on consensus from a group of APDS experts that [redacted], and that B cell makeup is important to lower the risk of infections and need for IRT, which in turn has positive impacts on patients' everyday activities and their lives in general.[55]

This view by regulatory bodies is supported by consistent clinician input. In an advisory board from April 2021, UK advisors expressed that lymphoproliferation requires active management in order to avoid progression, and the presence of lymphadenopathy helps determine which treatment a individuals with APDS initially receives.[5]

APDS experts and regulators have reached consensus that naïve B cells and lymphadenopathy are clinically meaningful endpoints, which influence clinician decision-making in the short-term and translate into long-term benefit. While this consensus was partially based on knowledge of the PI3Kδ pathway and clinician experience, it is supported by the available data, described below.

Immunophenotype changes

Results from the leniolisib clinical trials

Restoration of immune system functioning, a treatment goal in APDS, is demonstrated through normalisation of the immunophenotype and immunoglobulin (Ig) abnormalities classically present in individuals with APDS. Considering a threshold of ≥58.0% (see Table 5)[56] for normal naïve B cells as a percentage of total B cells, Study 2201 Part II included 19 participants in the leniolisib arm and eight in the placebo arm with abnormally low naïve B cells at Baseline. By Day 85, 74% of participants receiving leniolisib achieved normal levels of naïve B cells, versus 14% of participants who received placebo.[57]

Overall, the immunophenotype improvements at the end of Study 2201 Part II were maintained out to the last timepoint of sampling in Study 2201E1, with naïve B cell increases to 66.21% for leniolisib-treated patients at Day 85 of Study 2201 Part II, and 74.22% at Day 252 of Study 2201E1.[33, 36]

Benefits of immune system normalisation

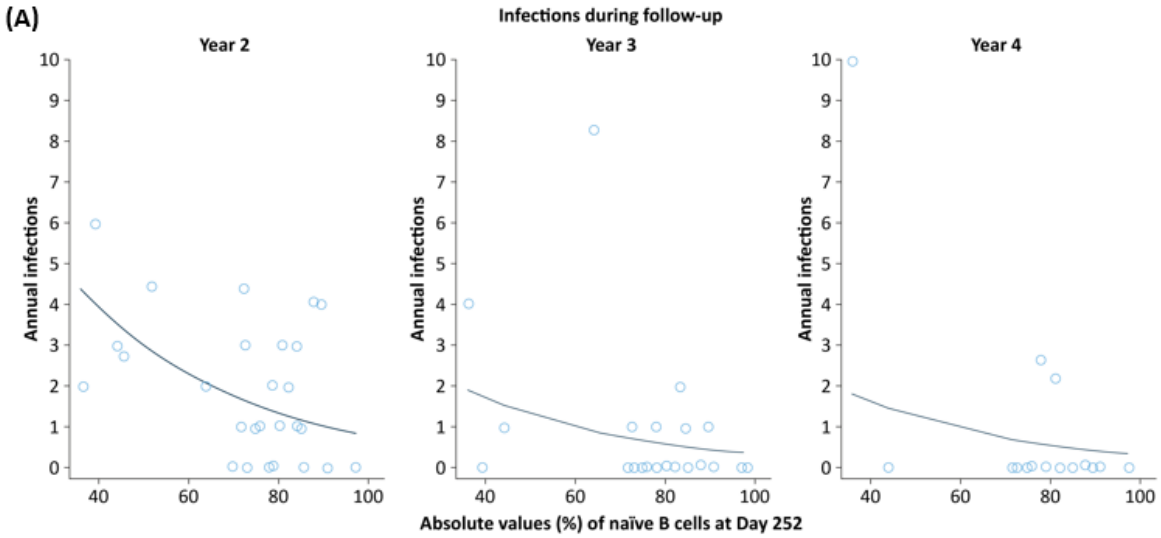
The benefit of a normalised immune system is reduced risk of infections, autoimmune disease and malignancy. As presented in Document B, Section B.2.6.1, evidence supporting this clinical convention may be observed in post-hoc analysis of data from Study 2201E1 showing a statistically significant correlation between increased naïve B cell percentage (of total B cells) at Day 252 with decreased infection rate in subsequent years (p=0.001; Table 3 presents the results of the analysis). The number of infections for Years 2, 3 and 4 was modelled based on a negative binomial model with the number of infections in Year 1 as a baseline reference value and change from baseline (Study 2201 Part II, study Day 1) to Day 252 in percentage of naïve B cells as a covariate. An increase in naïve B-cells was a significant predictor of a reduction in infection rates, with an estimated 2.3% reduction in the annual infection rate per 1% difference in the change from baseline in percentage of naïve B cells. Figure 1 presents a scatter plot of numbers of infections by year together with the fitted model for the mean number of infections plotted on the absolute scale.[58]

Table 3. Annualised infection rate model: the effect of change from baseline to visit 506 (V506) in proportion of naïve B cells (out of total B cells; main effects)

	IRR	LCI	UCI	P-value
Naïve B-cells	**0.977**	**0.966**	**0.988**	**0.001**
Year 1	1.000			
Year 2	0.816	0.509	1.307	0.398
Year 3	0.337	0.178	0.636	0.001
Year 4	0.325	0.136	0.774	0.011
Intercept	1.754	1.072	2.872	0.025

Abbreviations: IRR: incidence rate ratio; LCI: lower 95% confidence interval; UCI: upper 95% confidence interval.
Source: Pharming Data on File, 2024.[58]

Figure 1. Correlation of percentage of naïve B cells and infections in Study 2201E1



Footnote: The number of infections for Year 2, 3 and 4 were modelled based on a negative binomial model with the number of infections in Year 1 as a baseline reference value and change from baseline (Study 2201 Part II, study Day 1) to Day 252 in the percentage of naïve B cells as a covariate.
Source: Pharming Data on File, 2024.[58]

Normalised immunophenotype allows individuals to develop immune memory and normal immune response (just as is observed after a successful HSCT),[59, 60] leading to reductions in infection rate over years. However, improvement in naïve B-cells also has short-term benefits and is a driver of clinician decision-making. Looking from baseline to Day 85 in the placebo-controlled Part II, the effect of treatment on PtGA was assessed by adjusting for the change from baseline in naïve B-cells, with linear regression modelling (see Table 4). The proportion of treatment effect on PtGA explained by naïve B-cells was estimated to be 89%, confirming immune system normalisation as a patient-relevant benefit.[58]

Table 4. Results for the linear regression modelling to investigate the effect of leniolisib on PtGA when adjusting for the CfB in naïve B cells to Day 85

Covariate	Coefficient	Lower CI	Upper CI	p-value
Naïve B cells	0.52	-0.07	1.11	0.084
Treatment	2.08	-22.47	26.63	0.863

Source: Pharming Data on File, 2024.[58]

To the company's knowledge, naïve B cells have not been evaluated during regulatory approvals or other health technology assessments in other conditions. There are only two therapies licensed specifically for primary immunodeficiencies: Strimvelis® (a gene therapy for ACA-SCID) and IRT. As detailed in the CS in Document B, Section B.2.6.3, IRT is simply supplementation with donor antibodies and has no impact on immunophenotype, and therefore levels of naïve B cells would not have been measured.

Other studies of IEIs have shown a relationship between B-cell phenotype and clinical outcome, although not specifically naïve B-cells. Common variable immunodeficiency (CVID) is the most common IEI affecting adults, and is characterised by recurrent respiratory tract infections with up to 40% of patients also experiencing GI disease, lymphoproliferative disorders, autoimmunity, or granulomatous inflammation often in the lungs. In CVID, lack of antibody production is due to a

deficiency of switched memory B cells, whereas naïve B cells are generally at or above normal levels.[61] As such, almost all CVID studies find no association between naïve B cells and clinical outcome, but two studies observed a relationship prior to the first description of APDS in 2013[62] (relevant as some APDS patients had been previously diagnosed as having CVID)[63]:

- One study of 61 adult patients with CVID (2008 to 2012) found that naïve B cell counts were significantly lower in people with an interstitial lung disease (ILD) score >5, which is clinically significant.[64]
- Another study of 49 children with early-onset CVID (1995-2011) compared groups with accumulated transitional B cells (and lower proportion of mature B cells including naïve B cells) with people with accumulated naïve B cells (with lower proportion of more-mature B cells), and found that the group with lower naïve B cells had significantly higher prevalence of enteropathy (55.6 % vs 12.5 %, p=0.0201), granuloma formation (33.3 % vs 0 %, p=0.0154, with most cases in the lungs), production of monoclonal or oligoclonal IgM (44.4 % vs 8.3 %, p=0.0342), as well as combined features of cytopenia and lymphoproliferation or cytopenia and enteropathy (both 44.4 % vs 4.2 %, p=0.0133).[65]

Again, these results should be interpreted with caution, as CVID is generally not known to impact naïve B cells, and understanding of the role of genetics in IEIs has increased significantly since those studies. However, in general, immunophenotype is significantly associated with symptoms and severity. As CVID is characterised by deficiencies in switched memory B cells, several studies have found that the severity is associated with the degree of deficiency in CVID:

- Four studies found that lower switched memory B cells was associated with significantly higher risk of developing GLILD among a CVID cohort.[66-69]
- Three studies found significantly lower switched memory B cells for people with lymphoproliferation, autoimmunity, and/or chronic enteropathy when compared with CVID patients without these manifestations.[67-69]
- One study found significantly lower switched memory B cells in patients with bronchiectasis vs those without in a wider CVID cohort.[70]
- One study found a trend for lower switched memory B cells for patients with lymphoma, among a wider CVID cohort.[66]
- One study found no significant difference in switched memory b cells for people with CVID with or without autoimmunity.[71]
- One study found a trend for lower switched memory B cells in campylobacter patients vs those without.[72]

Lymphoproliferation

As described previously, reduction of lymphoproliferation is a treatment goal on its own. Physicians treat lymphoproliferation to relieve often debilitating symptoms resulting from swollen lymph nodes, which significantly impact quality of life.[46, 73-75]

Lymphadenopathy results from clinical trials

The 12-week blinded randomised placebo-controlled trial (RCT; Study 2201 Part II) of leniolisib showed a highly statistically significant reduction in size of lymphadenopathy, the key manifestation of lymphoproliferation, for leniolisib compared to placebo (first co-primary endpoint: difference in change from baseline for the index lesion log10 transformed sum of product of diameters [SPD] −0.25; p=0.0006). This finding translated to a 43.3% (p=0.0018) reduction in index lesion SPD for individuals receiving leniolisib vs placebo.[8, 32, 40] The open label extension study (OLE; Study 2201E1) showed the changes in leniolisib-treated patients to be durable, with

effects persisting until the last timepoint of radiological evaluation (Day 168 or 252, mean [SD] change from baseline of -49.5% (37.5), N=30).[40]

A supplementary Delphi panel with 23 clinicians with experience in managing individuals with APDS or PID estimated that for index lesion SPD, a median reduction of ≥20% in adults and ≥25% in adolescents (<18 years of age) within three months of treatment, would be considered clinically meaningful in APDS.[76] Nearly all (89%) leniolisib-treated participants in Study 2201 Part II experienced such improvement compared to 25% of participants receiving placebo; a treatment difference of 64% (nominal p=0.0022) in individuals receiving leniolisib vs placebo.[40] Sensitivity analyses using alternative thresholds yielded very similar results, demonstrating the certainty of the clinically significant treatment effect.

The clinically meaningful measure of lymphoadenopathy has also been reported by individuals with APDS. While not systematically evaluated in Study 2201, a detailed review of study subject narratives and interviews (with investigators, study subjects and carers) from both blinded Study 2201 Part II and Study 2201E1 periods (SPROUT analysis) showed that respondents, unprompted, reported improvements in these symptoms, including dysphagia, local pain and restricted neck movements – highlighting the clinical benefits of lymph node reduction.[43, 77]

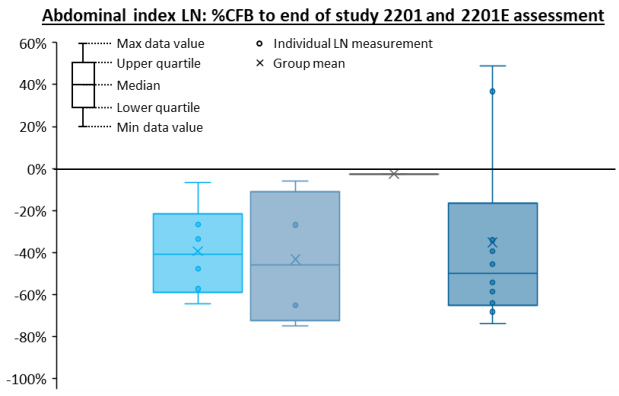
Other post-hoc results from Study 2201 Part II indicate an association between change in index lesion SPD and patient global assessment (PtGA) (correlation coefficient, -0.364, p=0.034). In this analysis, SPD responders (≥25% reduction in SPD at three months) achieved a mean (SD) 13.6 (19.4) point improvement in PtGA score, compared with a 4.9 (28.6) point decrease in those who did not.[57, 58] This indicates relief from the local effects of lymphadenopathy and likely APDS symptoms overall, that occur in tandem with lymph node size reduction.

Other manifestations associated lymphoproliferation

Experts agree that [redacted].[78]

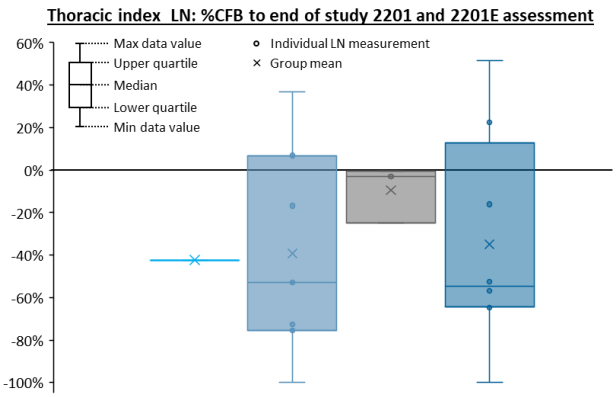
In Study 2201 Part II, lymphoproliferation in the spleen (which can cause significant discomfort, functional disability, increased risk of complications with trauma and cytopenias),[79-82] also saw significant reductions in size and volume, with RCT secondary endpoints being met by spleen volume at Day 85 vs placebo -186360.80 mm^3 (p=0.0020). This translated to a 25.3% reduction in participants receiving leniolisib compared to those receiving placebo (p=0.005).[8, 57] Reductions in lymph node size were seen in all leniolisib-treated patients in Study 2201 Part II and were detectable across all lymph node regions evaluated, including importantly, in thoracic (18% of participants) and abdominal (14% of participants) lymph nodes.[33, 34, 36]

Figure 2. Abdominal and thoracic index lescions at the end of Study 2201 and Study 2201E1



	Leniolisib part 1	Leniolisib part 2	Placebo part 2	OLE
# of patients	4	3	1	7
# of nodes	6	4	1	10
%CFB, mean ± SD	**–39% ± 0.21**	**–43% ± 0.32**	**–3%**	**–35% ± 0.43**
%CFB, min–max	–7% to –64%	–6% to –75%	–3%	+49%* to –68%

**Patient 1001009: at the OLE assessment, an increase in the size of 2 abdominal LNs was observed (overall CFB in total SPD of index nodes = +7%)*



	Leniolisib part 1	Leniolisib part 2	Placebo part 2	OLE
# of patients	1	5	2	6
# of nodes	1	7	3	8
%CFB, mean ± SD	**–42%**	**–39% ± 0.50**	**–9% ± 0.13**	**–35% ± 0.50**
%CFB, min–max	–42%	+37%# to –100%	0% to –25%	+52%#,‡ to –100%

#Patient 4001002: one thoracic LN increased in size at the D85 and OLE assessments; a second thoracic LN decreased in size at both assessments. The overall CFB in total SPD at was -51% and -43% at D85 and the OLE assessment, respectively; ‡Patient 1001023: at the OLE assessment, an increase in the size of a thoracic LN was observed (overall CFB in total SPD of index nodes = -30%)

Source: Study 2201 Part I CSR, Novartis 2017,[34] Study 2201 Part II CSR Version 2.0, Novartis 2022,[36] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023.[33]

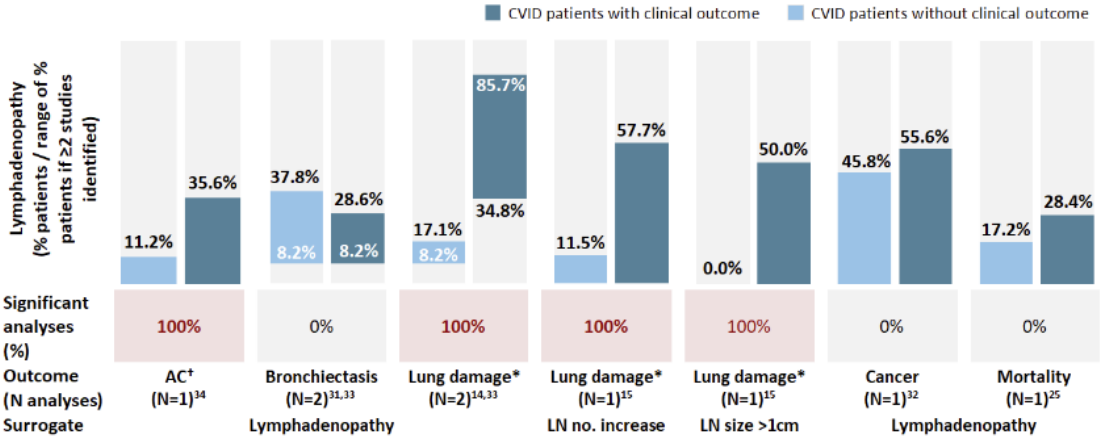
Evidence from a survey of 30 physicians treating individuals with APDS within the EAP and SPROUT review shows that leniolisib reduces the impact of the manifestations and sequelae of NLH.[29, 77] As reported in Document B, Section B.2.6.8, at least meaningful improvements in the EAP dataset were reported across gastrointestinal manifestations (including diarrhoea, colitis and rectal bleeding) 84% and pulmonary manifestations (including bronchiectasis, obstruction and dyspnoea) 53% in whom manifestations were noted before starting leniolisib treatment.[29] These extensive lymphoproliferation-related clinical responses are durable, as evidenced by the lack of worsening in any manifestation in participants who have administered treatment for a minimum of two years (33% of participants) and for whom meaningful improvements in manifestations on treatment had been recorded.[57]

Significant reduction in lymphoproliferation should be considered clinically meaningful, particularly when present in the gastrointestinal tracts, thoracic lymph nodes and spleen, as they are indicative of a decrease in disease activity. The breadth of data available on leniolisib show large reductions in lymphadenopathy at all sites, including abdominal and thoracic regions and the spleen and in lymphoproliferation-related symptoms. These effects are observed even in individuals with severe and/or advanced APDS and demonstrate the clear clinical benefits of treatment with this medicine.

Association between clinical trial endpoints and patient-centred clinical outcomes

A systematic literature review (SLR) was conducted to identify evidence on the associations between the clinical trial endpoints and patient-centered clinical outcomes in both APDS and proxy indications. While no studies were found for APDS, there were evaluations in CVID (a condition characterised by low levels of antibodies). Two studies of CVID patients found significant associations between lymphadenopathy and autoimmune cytopenia and lung damage, with a trend for increased risk of cancer (Figure 3). Relationships were also found between outcome and splenomegaly, with significant increases in autoimmune cytopenia and lung damage, with a trend towards increased risk of malignancy (Figure 4).[83]

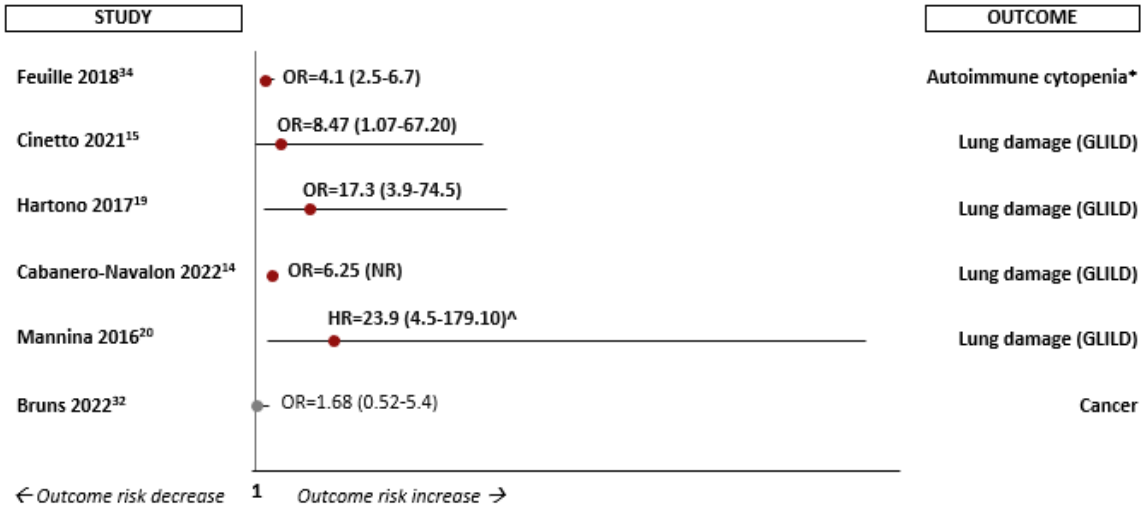
Figure 3. Association between lymphadenopathy and clinical outcomes



† Including the following diagnoses or variations of these: immune thrombocytopenia (ITP), hemolytic anemia (autoimmune hemolytic anemia, coombs + anemia, immune anemia), autoimmune neutropenia, Evans syndrome.
* Lung damage includes proxy outcomes of GLILD (n=1 analysis) and ILD (n=1 analysis).
Abbreviations: AC, autoimmune cytopenia; CVID, common variable immunodeficiency disorder; ITP, idiopathic thrombocytopenic purpura; LN, lymph nodes.

Footnotes: red markers = lymphadenopathy occurrence – significant outcome risk increase; grey markers = association between lymphadenopathy and clinical otucome not statistically significant.* Including the following diagnoses (or variations of these): immune thrombocytopenia (ITP), hemolytic anemia (AIHA, coombs + anemia, immune anemia), autoimmune neutropenia, Evan's syndrome.
Abbreviations: AIHA, autoimmune hemolytic anemia; CI, confidence interval; GLILD, granulomatous lymphocytic interstitial lung disease; ITP, immune thrombocytopenia (idiopathic thrombocytopenic purpura); OR, odds ratio.
Source: Pharming Data on File, 2024.[83]

Figure 4. Association between splenomegaly and clinical outcomes

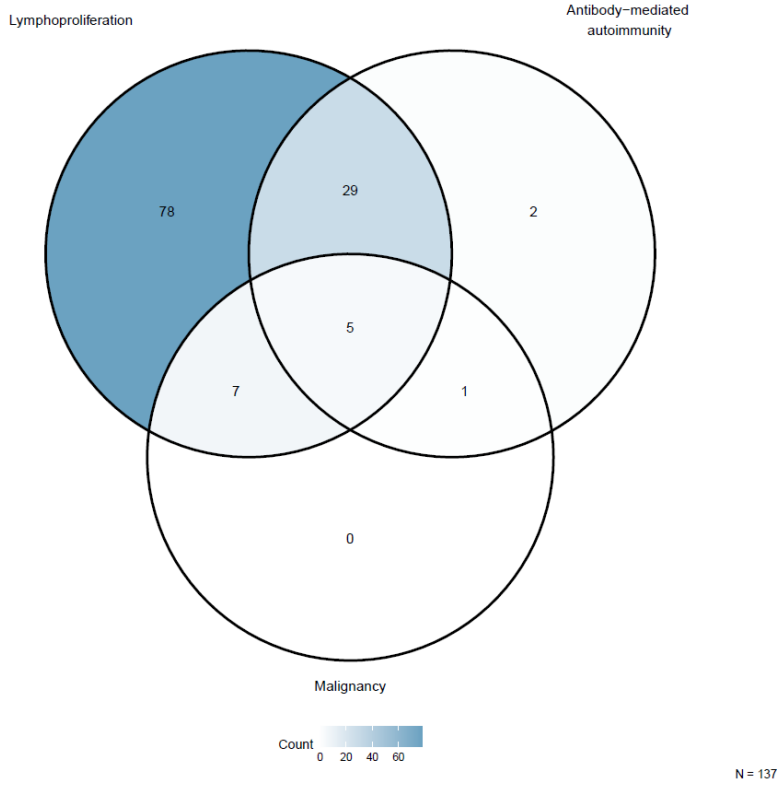


Legend: red markers = lymphadenopathy occurrence – significant outcome risk increase; grey markers = association between lymphadenopathy and clinical otucome not statistically significant.
* Including the following diagnoses (or variations of these): immune thrombocytopenia (ITP), hemolytic anemia (AIHA, coombs + anemia, immune anemia), autoimmune neutropenia, Evan's syndrome.
^ For an association between hypersplenism and lung damage (GLILD).
Abbreviations: GLILD, granulomatous lymphocytic interstitial lung disease; ITP, immune thrombocytopenia (idiopathic thrombocytopenic purpura); HR, hazard ratio; OR, odds ratio.

Source: Pharming Data on File, 2024.[83]

These findings are consistent with analysis of individuals with APDS in the ESID registry (November 2023 dataset), where 92% of individuals with APDS with malignancy also had a history of lymphoproliferation (Figure 5).[14]

Figure 5. A record of manifestations associated with lymphoproliferation for individuals with APDS in the ESID registry (November 2023 dataset; N=137)



Source: Pharming Data on File, 2023.[14]

Conclusion

Overall, based on evidence from the clinical trials and EAP, expert consensus, and opinion from other regulatory bodies, the clinical meaningfulness of measuring the percentage of naïve B cells (of total B cells) and lymphadenopathy in individuals with APDS is clear. Furthermore, both of these co-primary endpoints are associated with wider and long-term benefits in individuals with APDS, benefits of relevance to patients.

A8. Priority question: The B-PB analysis set included patients with fewer than 48% of naïve B cells at baseline to evaluate the efficacy of leniolisib.

a) **Can you please clarify the rationale for selecting a <48% threshold for inclusion in the primary analysis and discuss the limitations?**

b) **We understand B-cell counts are age-dependent and possibly transient therefore please comment on whether this threshold is equally valid for all included patients.**

a) As described in the response to question A.7, [redacted].[78]

In Study 2201, the threshold of naïve B cells (out of total B cells) at Baseline for the primary analysis was based on the lowest normal range for these cell levels reported in the literature. A complete examination of the composition of the B and T cell compartments was conducted in 145 healthy children and adolescents aged 0–18 years in the Netherlands.[84] Since the natural history ranges of B cell populations in people with APDS were not known during the design of Study 2201, a threshold value was set as 48% in Study 2201. This is the lowest value in the 6–9 years age range and the lowest across all ages 0–18 years reported by van Gent et al., 2009. Table 5 presents the lowest values reported by van Gent et al., 2009 alongside those from Morbach et al., 2010, which show considerable similarity.[56, 84]

The choice of threshold for the leniolisib clinical trials is not seen as a limitation, as in Study 2201 Part II, the pre-specified supportive analysis in the full PD analysis set (regardless of baseline naïve B cell levels) also showed a statistically significant improvement from Baseline in the proportion of naïve B cells of total B cells at Week 12 (difference in adjusted means: 27.94, SE: 6.09, [95% CI: 15.02, 40.85], p=0.0003).[8, 36] This result was consistent with the primary analysis in Study 2201 Part II where a statistically significant increase from Baseline to Week 12 (Day 85) in naïve B cells as a percentage of total B cells was observed in participants with fewer than 48% naïve B cells out of total B cells at baseline (difference in adjusted means: 37.30, SE: 5.74, [95% CI: 24.06, 50.54], p=0.0002).[8, 36] Therefore, whether using a 48% naive B cell threshold or considering data from all participants, there was a clear trend toward normalisation of the naive B cell immunophenotype beginning at one month of leniolisib treatment, which continued with extended leniolisib use.[33]

b) Among the adolescents and adults from both van Gent et al., 2009 and Morbach et al., 2010, the ranges observed did not differ greatly with age (see Table 5).

Table 5. Lower range value of the percentage (%) of naïve B cells out of total B cells in the adolescents and adults in the general population

Source	Lower range of % naïve B cells out of total B cells			
	12–15 years	15–18 years	19–25 years	26–50 years
van Gent et al., 2009	64.6%	59.0%	NR	NR
Morbach et al., 2010	75.2%[a]		65.6%	58.0%

Footnotes: [a]This is the lowest value of the range for naïve B cells out of total B cells for ages 11–18 years of age.
Abbreviations: NR: not reported.
Source: Morbach et al., 2010[56] and van Gent et al., 2009.[84]

In individuals with APDS, abnormality in the proportions of naïve B cells out of total B cells is not transient. In Study 2201 Part II, among the 10 participants that were in the placebo group and had at least one measurement of the proportion of naïve B cells out of total B cells in addition to the baseline measurement, the median baseline percentage of naïve B cells was 37%; the change from Baseline at each follow-up measurement is shown in Table 6.

Table 6. Naïve B cell proportions for participants who received placebo in Study 2201 Part II and continued leniolisib treatment in Study 2201E1

Study	Study 2201 Part II (placebo group)			Study 2201E1 (on leniolisib)			
Day	Day 29	Day 57	Day 85	Day 1	Day 84	Day 168	Day 252
n	9	9	10	9	7	7	7
Median CfB[a]	–2.1	1.1	1.4	–2.5	37.4	38.9	43.1
Median naïve B cells as % of total B cells	42	35	32	26	66	80	86

Footnotes: [a]Change from baseline in naïve B cells as a % of total B cells.
Abbreviations: CfB: change from baseline.
Source: Study 2201 Part II CSR Version 2.0, Novartis 2022 (Listing 16.2.6-8.1b),[36] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Listing 16.2.6-1.10).[33]

Based on these data and the lifelong recurrence of oto-sinopulmonary infections experienced by people with APDS,[10, 14] the company has no reason to believe that the reduced proportion of naïve B cells out of total B cells is temporary or transient, or that levels fluctuate substantially over time (Table 6). Leniolisib is the first targeted treatment for APDS that leads to normalisation of the immunophenotype, a finding which should have been observed with non-targeted treatments if indeed naïve B cell reductions were transient.

In conclusion, as shown by the pre-specified supportive analysis of Study 2201 Part II and Table 6 above, the exact numerical cutoff for "normal" levels of naive B cells is less critical than the observation that participants on leniolisib are experiencing sustained immunophenotype normalisation at a high rate, compared to infrequent or no normalisation with current clinical management. The influence of age on the proportion of naïve B cells out of total B cells appears minimal, as evidenced by consistent ranges observed in adolescents and adults from van Gent et al., 2009 and Morbach et al., 2010.[56, 84] Moreover, the company has no reason to believe that the reduced proportion of naïve B cells is temporary or transient.

A9. We note the results from semi-structured interviews detailed in the document filed as *Pharming_Delphi Report_Meaningful Change_v4_1Mar2024*. Please clarify whether the sample of clinicians (n=9) who took part in the interviews are different to those who took part in the Delphi; what number had direct experience treating patients with leniolisib and their area of clinical expertise (e.g. paediatric immunologist).

The company can confirm that the clinicians interviewed ahead of the Delphi panel were different from those that participated in the Delphi panel. The selection strategy aimed to include individuals with specific expertise in various areas; specifically to enlist some clinicians with expertise in APDS, some specialising in lymphadenopathy, and some focusing on B cells. Clinicians in the latter two categories could come from fields outside of immunology. Efforts were made to limit the number of clinicians who were trial investigators or had firsthand experience with the drug.

Table 7 presents the expertise and experience of the clinicians involved in the Delphi panel. In total, 23/24 (96%) had seen at least one APDS individual in their career.[5] The company did not select panelists for their experience treating with leniolisib, but rather for their experience in treating APDS, as the results of the Delphi panel are treatment agnostic and apply to any treatment for APDS.

Table 7. Listed expertise of clinicians involved in the Delphi panel

Background variable	Descriptive statistic (n=24)
Location	88% United States 4% Canada 4% UK 4% Italy
Specialty Area	96% Allergy/Immunology 4% Haematology/Oncology 33% mention “pediatric” in their specialty area
Primary Immunodeficiency (PI) Treatment History	Number of PI patients treated **in past year**: Mean= 183.3, median= 135, range= 0–500 Number of PI patients treated **in career**: Mean= 1311.5, median= 800, range= 0–5000
APDS Treatment History	Number of APDS patients treated **in past year**: Mean= 2.5, median= 2, range= 0–10 Number of APDS patients treated **in career**: Mean= 5.5, median= 3.5, range= 0–25
Familiarity with APDS (0–10 scale)	Mean= 8.9, median= 9, range= 6–10

Source: Pharming Data on File, 2023.[76]

A10. Priority question: It appears that thresholds for a clinically meaningful difference of lymphadenopathy in adults at 3 months vary across documents. For example:

- **≥20%; Document B, section B.2.4.2, table 12)**
- **>26.56%; Results from the Delphi survey (table 2)**
- **>25%; Ad-Hoc Expert Group (AHEG EMEA) meeting**

a) **Please could you clarify, if these thresholds relate to the same endpoint definitions? If there are differences between the thresholds, can you provide justification for these differences and state the implications?**

b) **If there are differences between the endpoint definitions used, please could you clarify these differences.**

The company would like to note that the threshold presented in Table 12, Document B, Section B.2.4.2 (i.e. ≥20% for adults and ≥25% for adolescents) is the threshold that was utilised throughout the CS; this is the median threshold from the final round (Round 5) of the Delphi panel.[76]

Table 8 presents the thresholds for a meaningful improvement in index lesion SPD (lymphadenopathy) after three months of treatment, in Round 5 of the Delphi.[76] Throughout the CS, the company utilised the estimated **median** values from the Delphi panel due to the relatively small sample size of clinicans and the potential for outliers to substantially impact mean values. However, as shown in Table 8, the estimated mean and median values were similar.

Table 8. Estimated mean and median threshold values for a meaningful improvement in index lesion SPD after three months of treatment in individuals with APDS (Round 5 of a Delphi panel)

	Mean	Median (utilised in CS)
Adults at 3 months	26.56%	20%
Adolescents at 3 months	24.69%	25%

Abbreviations: SPD: sum of product diameters.
Source: Pharming Data on File., 2023.[76]

The ad-hoc expert group (AHEG) meeting with the European Medicines Agency (EMA) was held on the 27th November 2023, and the briefing document solely reported the interim (Round 4) results of the Delphi study. The CS instead utilised the thresholds from the final round of the Delphi study (Round 5), which can all be found in Table 2 within the Delphi report labelled as "*Pharming_Delphi Report_Meaningful_Change_v4_1Mar2024*" in the reference pack.

Trial evidence – generalisability

A11. The clinical trial 2201 Part II does not appear to include any participants from England. Can you comment on the generalisability of the findings to the UK population? Specifically, are you aware of any differences in the standards of care received in participating trial sites?

The company strongly believes that the trial population in Study 2201 Part II is representative of the UK population, with findings of the study generalisable to UK clinical practice, and the standard of care treatments prescribed are consistent across participating trial sites.

Study 2201 Part II population is considered generalisable to the UK population

In Exercise 3 of the Expert Consultancy, all four clinicians based in England unanimously agreed that the baseline characteristics in Study 2201 Part II were generalisable to the individuals with APDS that they see in routine clinical practice.[6] Despite the absence of a trial site in England, the ten study centres for Study 2201 were spread across the UK (Belfast), six European countries, the United States of America and the Russian Federation (a site in Moscow),[33, 34, 36] all of which are expected to have demographics similar to the UK population. To supplement clinical opinion from the Expert Consultancy, the company has analysed data from UK individuals with APDS in the ESID registry, who consented to share data with industry, to investigate their demographics, clinical characteristics and medication use (data cut-off: 6th November 2023). These analyses could not be performed specifically for English individuals as the ESID database does not report on individual countries within the UK. However, of the individuals with APDS in UKPID registry (a major contributor of the ESID registry), [redacted] are from England (as of 30th April 2024). Therefore, the vast majority of individuals with APDS in the ESID registry are from England.

Demographic characteristics

As shown in Table 9, demographic characteristics including age and sex for participants in Study 2201 Part II at Baseline were comparable to UK individuals with APDS in the ESID registry.

Table 9. Demographic characteristics for participants enrolled in Study 2201 Part II at Baseline and known UK individuals in the ESID registry

	Study 2201 Part II	ESID Registry (UK Population)[a]
Total participants that completed the study – n	31	26
Age (years) – mean (SD)	23.7 (11.19)	At registration: 24.6 (13.0) At last follow-up: 26.0 (13.1)
Participants under 18 – n (%)	12 (38.7)	At registration: 8 (30.8) At last follow-up: 8 (30.8)
Sex – n (%) Male Female	 15 (48.4) 16 (51.6)	 16 (61.5) 10 (38.5)
Predominant Race – n (%) White Asian Black (or African American for Study 2201E1) Other	 25 (80.6) 2 (6.5) 2 (6.5) 2 (6.5)	NR
Ethnicity – n (%) Hispanic or Latino Not Hispanic or Latino NR	 1 (3.2) 21 (67.7) 9 (29.0)	NR
Weight (kg) – mean (SD)	66.92 (14.259)	At registration: 53.5 (21.5)[b]
Height (cm) – mean (SD)	164.13 (8.208)	At registration: 154.8 (18.6)[c]
BMI (kg/m^2) – mean (SD)	24.80 (4.811)	At registration: 22.3 (5.4)[c]

Footnotes: [a]Data cut-off for data from the ESID registry: 6th November 2023. [b]N=25 (96.2), [b]N=24 (92.3).
Abbreviations: NR: not reported.
Source: Pharming Data on File., 2023[14] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023[33] and Rao et al., 2023.[8]

Clinical characteristics

Due to minor differences in definitions and reporting formats, the company categorised clinical characteristics into broader groups for comparison between Study 2201 Part II and the ESID registry in Table 10. Baseline clinical characteristics, including prior manifestations, for participants in Study 2201 Part II were similar and generally in line with those seen in UK individuals with APDS in the ESID registry. History of neoplasms (benign, malignancy and unspecified), gastrointestinal disorders and surgical and medical procedures were more prevalent in the trial population; however, this should not affect any interpretations or conclusions:

- The differences between the trial population and UK individuals with APDS from the ESID registry are likely due to inherent variability seen within small sample sizes, and are expected to have minimal impact on the validity and generalisability of the results.
- There may also be discrepancies between the two sources in terms of consistency of reporting and in definitions for the manifestations/procedures. Clinical trials may record manifestations/procedures more comprehensively and consistently than retrospective observational studies, for example.

Table 10. Clinical characteristics for participants enrolled in Study 2201 Part II at Baseline and known UK individuals in the ESID registry

	Study 2201 Part II (N=31)	ESID Registry (UK Population)[a] (N=26)
Disease type – n (%)	APDS1, 25 (80.6) APDS2, 6 (19.4)	APDS1, 20 (76.9) APDS2, 6 (23.1)
Lung function (respiratory, thoracic and mediastinal disorders) – n (%)	23 (74.2)	23 (88.5)
Infections and infestations – n (%)	29 (93.5)	25 (96.2)
Blood and lymphatic system disorders – n (%)	22 (71.0)	21 (80.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) – n (%)	11 (35.5)	5 (19.2)
Gastrointestinal disorders – n (%)	17 (54.8)	10 (38.5)
Surgical and medical procedures – n (%)	26 (83.9)	14 (53.8)

Footnotes: [a]Data cut-off for data from the ESID registry: 6th November 2023.
Abbreviations: APDS: activated PI3K delta syndrome; ESID: European Society for Immunodeficiencies.
Source: Pharming Data on File., 2023[14] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023[33] and Rao et al., 2023.[8]

As noted in the company submission, the clinical trial inclusion criteria required participants to present with nodal and/or extranodal lymphoproliferation, recurrent oto-sinopulmonary infections, and at least one measurable nodal lesion on a CT or MRI scan.[85] However, all five clinicians in Exercise 3 of the Expert Consultancy, including four based in England, agreed that most individuals with APDS would present with at least one measurable lymph node lesion, reinforcing the trial population's generalisability to UK clinical practice.[6]

Medication use

Medication use for participants at Baseline of Study 2201 Part II and individuals with APDS from the UK in the ESID registry is provided in Table 11. Baseline medication use was generally similar across Study 2201 Part II and the UK individuals within the ESID registry.

Between Study 2201 Part II and the ESID registry, use of glucocorticioids, antibiotic prophylaxis, IRT use, and previous sirolimus treatment were generally balanced (<15% difference). However, it should be noted that antibiotic prophylaxis and previous sirolimus treatment use are "unknown" in a large proportion of the UK APDS population from the ESID registry.

Table 11. Medication use for participants enrolled in Study 2201 Part II at Baseline and known UK individuals in the ESID registry

	Study 2201 Part II (N=31)	ESID Registry - UK Population[a] (N=26)
Glucocorticoid use – n (%)		
No	13 (41.9)	12 (46.2)
Yes	18 (58.1)	14 (53.8)
IRT use – n (%)		
No	10 (32.3)	11 (42.3)
Yes	21 (67.7)	15 (57.7)
Antibiotic prophylaxis – n (%)		
No	14 (45.2)	0 (0.0)
Yes	17 (54.8)	18 (69.2)
Unknown	N/A	8 (30.8)
Previous sirolimus treatment[b] – n (%)		
No	24 (77.4)	12 (46.2)
Yes	7 (22.6)	4 (15.4)
Unknown	N/A	11 (42.3)

Footnotes: [a]Individuals with APDS from the UK in the ESID registry with a record of treatment use (data cut-off: 6th November 2023).
Abbreviations: ESID: European Society for Immunodeficiencies; IRT: immunoglobulin replacement therapy; N/A: not available.
Source: Pharming Data on File., 2023[14] and Study 2201E1 CSR (IA2), Pharming Data on File, 2023[33] and Rao et al., 2023.[8]

EAP

Furthermore, findings from the company's EAP, as detailed in Document B, Section B.2, align with clinical trials regarding the efficacy and safety of leniolisib for treating APDS. This demonstrates the generalisability of the findings, particularly considering that [redacted] of total EAP population ([redacted] of EU EAP population) are individuals with APDS from the UK.[5]

Conclusion: baseline characteristics

In conclusion, demographic and clinical characteristics, as well as medication use for participants at Baseline in Study 2201 Part II are comparable to individuals with APDS from the UK in the ESID registry, suggesting that the trial population is representative and generalisable to the UK population.

There are no anticipated differences in standard of care treatments prescribed across trial sites

Across all participating trial sites in the pivotal Study 2201 Part II, the administration of permitted concomitant treatments adhered to a pre-defined protocol.[1, 86] All trial participants were allowed to continue receiving selected concomitant treatments, including: steroids (except glucocorticoids above 10 mg or 25 mg prednisone or equivalent per day within 2 weeks for Study 2201 Part I or Study 2201 Part II/Study 2201E1, respectively), antimicrobials, IRT, anilides (analgesics such as paracetamol),[87] propionic acid derivatives (e.g. non-steroidal anti-inflammatory drugs such as ibuprofen) and selective beta-2-adrenoreceptor agonists.[33, 36] The administration of these permitted concomitant treatments followed a clear protocol (defined in the Study 2201 Part II protocol, Section 6.9). Additionally, certain treatments were associated with a strict protocol-defined washout period prior to first dosing of the study medication (Section 9.3.2 in the clinical

study report of Study 2201 Part II).[36] Therefore, with all permitted concomitant treatments administered per-protocol and non-permitted treatments requiring a protocol-defined washout period, no anticipated differences in standard of care treatments are expected across trial sites.

Furthermore, there were no anticipated differences in the availability of concomitant treatments across the participating trial sites, as all permitted treatments were routinely used and consistently accessible in all the countries where participants were located.

Indirect treatment comparison

A12. Could you please justify the choice of covariates used in the indirect treatment comparison (Document B, section B.2.9 and corresponding Appendix N2.2).

The covariates for this study were selected based on their direct relevance to the research question, their biological significance in APDS, as well as being supported by existing literature and by the company's medical team as presented in Table 12.[39]

Table 12. Covariates included in Study 2201E1 and the ESID extenrally controlled indirect matched comparison

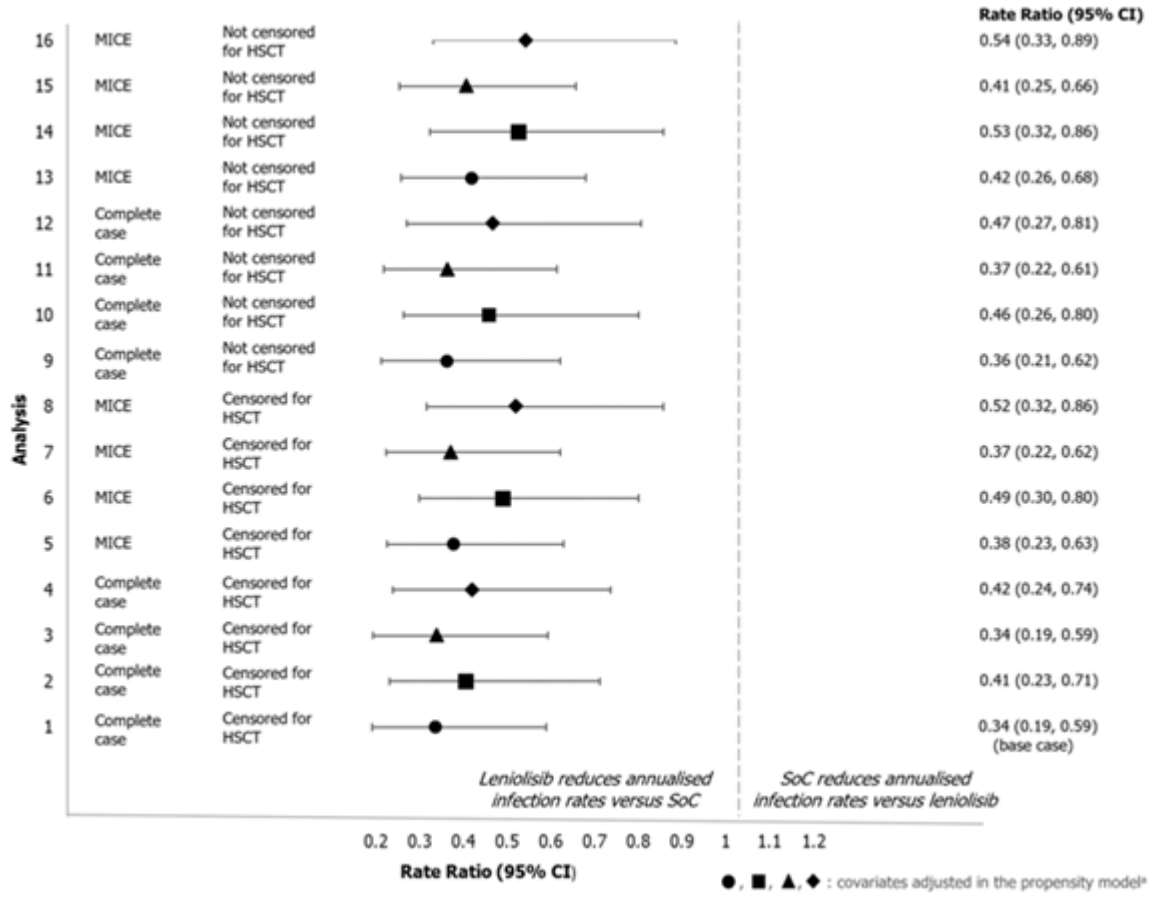
Covariate	Respiratory infection analysis	IgM analysis	Justification
Age	Y	N	Susceptibility to infections can vary with age. Infants and the elderly are generally more susceptible to infections due to their comparatively weaker immune systems. Serum IgM are relatively stable from the age of 12 and so were therefore not expected to impact the IgM analyses.[88]
Sex	Y	Y	Sex was included as a covariate based on the pre-defined subgroup analyses of Study 2201.[36]
APDS disease type	Y	Y	APDS disease type (or 'mutation status') was included conservatively, as it was not clear if infections or hyper-IgM would be present or treated differently in individuals with APDS1 vs APDS2.
Baseline infection rate	Y	N	Baseline infection rates were considered to be a proxy of disease severity, and were included in order to better balance the populations.
Baseline IRT	Y	N	Baseline IRT was included to identify initial differences in infection rates between groups and to isolate the effect of leniolisib.
Baseline IgM (g/L)	Y	Y	Baseline IgM was selected as a proxy for severity of illness (whereby a higher baseline IgM indicates higher severity illness).
Age at first IgM test	N	Y	Age at first IgM test was selected as a proxy for disease duration (whereby older age at baseline IgM test indicated longer duration of disease during follow-up).

Footnotes: **'Y'** indicates that the covariate was included in the analysis; **'N'** indicates that the covariate was not included in the analysis.
Abbreviations: IgM: immunoglobulin M; IRT: immunoglobulin replacement therapy.

Significant reductions in the annual rate of respiratory tract infections (rate ratio: 0.34; 95% confidence interval [CI]: 0.19, 0.59) and serum IgM levels (treatment effect: –1.09 g/L; 95% CI: –1.78, –0.39, p=0.002) were observed in leniolisib-treated individuals compared with standard of care, based on the findings of these analyses.[39]

The results were consistent in all sensitivity analyses (Figure 6) regardless of missing data handling, covariate selection, censoring at HSCT, or definition of the baseline infection rate, showing a consistent and statistically significant reduction of 46–66% in annual infection rates for participants treated with leniolisib.

Figure 6. Rate ratio (95%) CI for annualised infection rate for the treatment and control population across all sensitivity analyses[a]



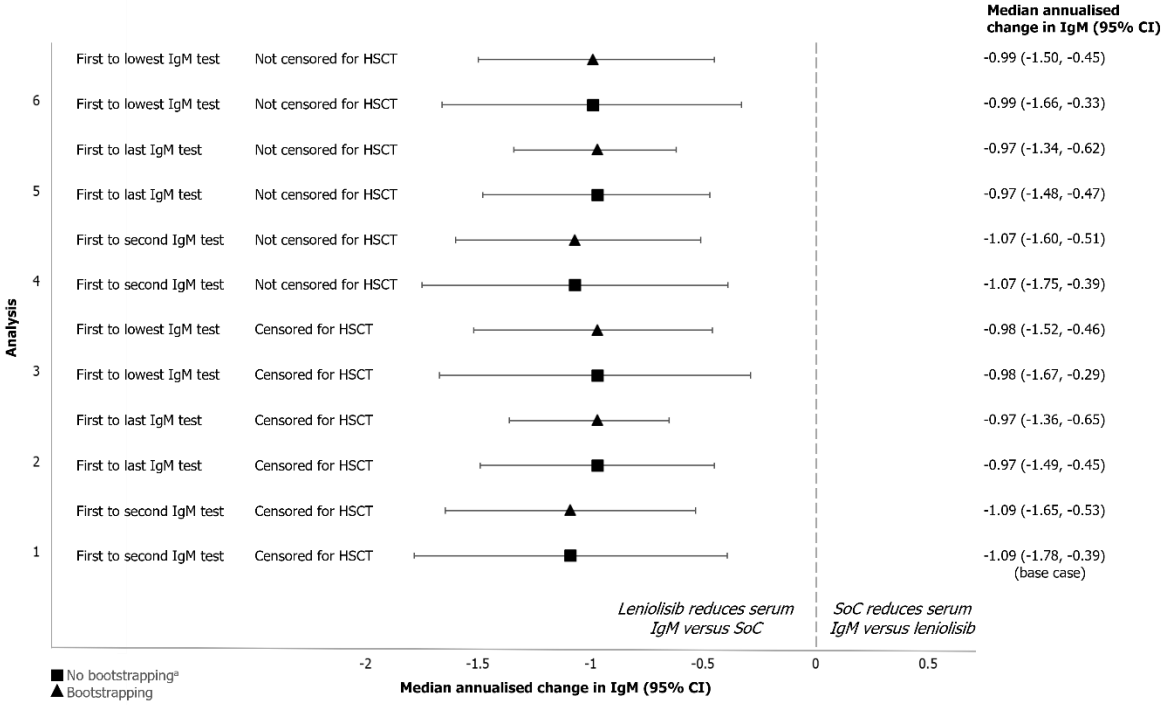
Footnote: [a]The symbols used in the figure indicate the covariates adjusted for in the propensity score model. ● Age, IRT use, baseline infection rate (within Study 2201 Part I/II for treatment population). ■ Age, IRT use, baseline infection rate (within first 183 days of OLE for treatment population). ▲ Age, IRT use, baseline infection rate (within Study 2201 Part I/II for treatment population), IgM, sex, APDS type. ◆ Age, IRT use, baseline infection rate (within first 183 days of OLE for treatment population), IgM, sex, APDS type. Analysis 1 is the base case for the respiratory infection analysis; analyses 2–16 correspond to the sensitivity analyses which can be found in the supplementary material of the manuscript included in the reference pack.

Abbreviations: CI: confidence interval; HSCT: haematopoietic stem cell transplantation; IgM: immunoglobulin M; SoC: standard of care.

Source: Whalen et al., 2024.[39]

Results were consistent in the sensitivity analyses exploring the definition of annualised change in IgM (Figure 7), using bootstrapping: comparing first to last IgM test for the control group resulted in a treatment effect of -0.97 g/L (95% CI: -1.36, -0.65, p=0.001) and comparing first to lowest test for IgM for the control group resulted in a treatment effect of -0.98 g/L (95% CI: -1.52, -0.46, p=0.003). Results were also consistent when censoring for HSCT was not performed.

Figure 7. Annualised change in IgM (95% CI) for the leniolisib versus control population across all sensitivity analyses



Footnote: [a]In all analyses, 95% CIs were calculated with and without the bootstrapping method.
Abbreviations: CI: confidence interval; HSCT: haematopoietic stem cell transplantation; IgM: immunoglobulin M; SoC: standard of care.
Source: Whalen et al., 2024.[39]

Concurrent use of some immunosuppressive medications were not permitted in Study 2201.[36] An additional sensitivity analysis was conducted, which excluded patients on immunsuppressants from the ESID registry, resulting in 14 complete cases in the control population. The rate ratio (95% CI) of respiratory tract infections for the leniolisib group vs controls was 0.24 (0.12, 0.50).[39]

Finally, as unknown confounders may exist, quantitative bias assessment was conducted. The resulting E-values suggest that any unknown confounder would need to have a stronger association with treatment outcome than any of the known confounders accounted for in our analysis. This is felt to be unlikely, given the large number (24) of sensitivity analyses conducted to evaluate different structural and modelling assumptions, and enrollment of participants in Study 2201 from countries participating in the ESID registry (with the exception of the United States).[39]

In conclusion, the covariates for this study were selected based on their direct relevance to the research question, their biological significance in APDS, and support from existing literature and the company's medical team. The results remained consistent across all sensitivity analyses for respiratory infections and IgM analyses, regardless of covariate selection.

Safety

A13. Other studies including approved PI3K inhibitors such as Umbalisib and Copanlisib have reported a number of grade 3 adverse events such as Pneumonia, Hyperglycemia, Diarrhea/colitis, Hepatotoxicity, Hyperglycemia, Hypertension,

Leukopenia, and Neutropenia. Could you please comment on how likely patients receiving leniolisib will also experience these adverse events compared to standard of care.

It is unlikely that people with APDS receiving leniolisib will experience these adverse events more frequently compared to individuals receiving current clinical management. This conclusion can be drawn from leniolisib's mechanism of action in the context of APDS being a PI3Kδ-driven disease (versus the oncology indications for other PI3K inhibitors), the specificity of leniolisib, and the extensive follow-up data from leniolisib clinical trials and the EAP.

Pathophysiology of APDS, and treatment mechanism of action

In individuals with APDS, a germline mutation results in elevated PI3Kδ activity.[10] Therefore, the primary goal of treatment in APDS is to normalise PI3Kδ pathway activity, in order to (in time) restore the APDS-associated immune dysregulation and immune deficiency.[89] The treatment goal in APDS is normalisation of the PI3Kδ pathway and not complete inhibition. Conversely, in oncology, tumor growth is driven by multiple signaling pathways, including PI3Kδ.[90] The goal of other PI3K inhibitors used in haematologic or solid cancers is to profoundly suppress the PI3K pathway in tumor cells for a maximal cytotoxic effect.[89, 91] Both copanlisib and umbralisib were used to treat haematological cancers.[92, 93]

Leniolisib differs from other PI3Kδ inhibitors due to its novel structure, which allows for specific inhibition of the PI3Kδ isoform and a unique mechanism of action:

- Umbralisib, which was used as a treatment for marginal zone lymphoma and follicular lymphoma, features a propeller shape that forms a specificity pocket within the ATP-binding site of PI3Kδ.[89, 93]
- Leniolisib however is structurally unique relative to other approved PI3Kδ inhibitors, as it is not propeller-shaped. The structure of leniolisib enables it to interact specifically with the tryptophan shelf at the edge of the ATP-binding site in PI3Kδ, conferring specificity for the PI3Kδ isoform (biochemical IC50s of 240, 424, 11, and 2230 nM at PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ, respectively.[89]
- In contrast, copanlisib (was indicated for treating adult patients with relapsed follicular lymphoma) is a pan-class I PI3K inhibitor, with predominant activity against both PI3Kα and PI3Kδ isoforms.[92]

In APDS, leniolisib selectively inhibits p110δ, resulting in normalisation of the PI3Kδ pathway by inhibiting the recruitment and activation of a range of messengers downstream of PI3Kδ.[2, 89] In the oncology setting, hyperactivity of the PI3Kδ pathway is confined to cancerous cells while non-malignant cells exhibit normal PI3Kδ activity. Therefore, although the PI3Kδ inhibitors in oncology aim to inhibit this pathway in tumour cells, these inhibitors also inadvertently reduce PI3Kδ activity in normal cells, which can lead to adverse events.[89, 91]

In summary, leniolisib distinguishes itself from other PI3Kδ and pan PI3K inhibitors through its unique structural features and specific inhibitory properties, selectively targeting the PI3Kδ isoform, in order to normalise pathway activity.[89] Therefore, it would be reasonable to assume that these PI3K inhibitors have incomparable safety profiles, particularly across their different indications.

Experience in practice

Experience in Study 2201

Immune-related adverse events (ir-AEs), such as serious diarrhoea/colitis, serious hepatotoxicity, serious infections, pneumonitis and severe cutaneous adverse reactions (SCAR), are considered a class effect for PI3K inhibitors. In oncology patients, ir-AEs appear usually within the first months of treatment, with the majority presenting within the first 30 days,[94] and continue to worsen or require drug discontinuation or interruption or dose reduction

Analysis of the safety data from Study 2201E1 did not reveal any events suspected as ir-AEs (no non-disease-related serious infections, no new severe diarrhoea/colitis, no hepatotoxicity, no pneumonitis, no serious cutaneous adverse reactions). Instead, the frequency of infections and other signs and symptoms in individuals with APDS treated with leniolisib gradually decreased over time and continued to decrease over the years.

Across the leniolisib clinical trials, 28.9% of participants treated with leniolisib experienced Grade 3 AEs.[37] Noteably, in Study 2201 Part II, 9.5% (2/21) of participants in the leniolisib group experienced Grade 3 AEs, compared with 30.0% (3/10) in the placebo group.[8, 36] Moreover, as illustrated in Table 13, the occurrence of these specific Grade 3 adverse events (pneumonia, hyperglycemia, diarrhea/colitis, hepatotoxicity, hyperglycemia, hypertension, leukopenia, and neutropenia) across the leniolisib clinical trials was low.[33] Specifically, Grade 1 adverse events 'liver disorder' and 'blood pressure increase' were both reported by 2.6% (1/38) of participants (the maximum toxicity reached was Grade 1). In the leniolisib clinical trials, 2.6% (1/38) of participants reported Grade 2 adverse events of 'diarrhoea' and 'neutropenia' (the maximum toxicity reached was Grade 2).[33]

Experience in the EAP:

[redacted].[95] These data are presented for completeness of information, although compassionate use may not represent standard of care as it includes patients who may not have qualified for a clinical trial, and may be on doses other than leniolisib 70mg bid.

An overview of the events per system organ class according to the reporter causality is provided in Table 14, with bold face denoting the events specifically referred to in clarification question A.13.

Table 13. Incidence of the specific AEs/TEAEs listed in A.13 at Grade 3 across the leniolisib clinical trials (safety analysis set)

	Study 2201 Part I			Study 2201 Part II		Study 2201E1 (leniolisib 70 mg bid)			Total Leniolisib N=38 n, (%)
	Leniolisib 10 mg bid N=6 n, (%)	Leniolisib 30 mg bid N=6 n, (%)	Leniolisib 70 mg bid N=6 n, (%)	Leniolisib 70 mg bid n=21 n, (%)	Placebo bid n=10 n, (%)	Previous Leniolisib n=26 n, (%)	Previous Placebo n=9 n, (%)	Total Extension N=37 n, (%)	
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0, 0 (0.0)	1 (2.7)	1 (2.6)
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.7)	1 (2.6)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.7)	1 (2.6)
Leukopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.7)	1 (2.6)

Footnotes: Under one treatment, a patient with multiple adverse events within a primary system organ class is counted only once in the total row, a patient with multiple occurrences of an adverse event is counted only once in the AE category, and a patient with multiple toxicity ratings for an AE under treatment, is only counted under the maximum rating. Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal. Only adverse events occurring at or after first drug intake are included.
Abbreviations: N = number of patients studied; n = number of patients with at least one AE in the category.
Source: Study 2201E1 CSR (IA2), Pharming Data on File, 2023 (Table 14.3.1-1.2).[33]

Table 14. Overview of AEs per system organ class according to causality, in the EAP (AEs specified in clarification question A.13 in boldface)

System organ class	PT	Serious		Non-serious		Total
		Related	Not related	Related	Not related	
Blood disorders	Lymphadenitis	0	1	0	0	1
	Lymphadenopathy	0	1	0	0	1
	Neutropenia	**0**	**0**	**1**	**0**	**1**
Gastrointestinal disorders	Abdominal pain	0	0	1	0	1
	Aphthous ulcer	0	0	1	0	1
	Diarrhoea	**0**	**0**	**0**	**1**	**1**
	Nausea	1	0	1	1	3
	Vomiting	1	0	0	1	2
General disorders	Chills	0	1	0	0	1
	Drug ineffective	0	0	1	0	1
	Pyrexia	0	0	1	0	1
	Therapeutic response shortened	0	0	1	0	1
	Therapeutic effect decreased	0	0	1	0	1
Hepatobiliary disorders	**Hepatic steatosis**	**0**	**0**	**1**	**0**	**1**
	Hyperbilirubinaemia	**0**	**0**	**1**	**0**	**1**
Infections and infestations	Giardiasis	0	0	1	0	1
	Infection	0	0	0	2	2
	Lower respiratory tract infection	0	1	0	0	1
	Norovirus infection	0	1	0	0	1
	Pneumonia	**0**	**1**	**0**	**0**	**1**
	Respiratory tract infection	0	0	0	1	1
	Sepsis	0	1	0	0	1
	Upper respiratory tract infection	0	0	0	1	1
Injury	Expired product administered	0	0	1	0	1
	Muscle strain	0	0	1	0	1
	Product dose omission issue	0	0	0	1	1
Investigations	**Amylase increased**	**0**	**0**	**1**	**0**	**1**
	C-reactive protein increased	**0**	**0**	**1**	**0**	**1**
	Hepatic enzyme increased	**0**	**0**	**3**	**0**	**3**
	Liver function test abnormal	**0**	**0**	**1**	**0**	**1**
	Liver function test increased	**0**	**0**	**1**	**0**	**1**
	Weight decreased	0	0	0	1	1
	Weight increased	0	0	1	0	1
Metabolism and nutrition disorders	Dehydration	1	0	0	0	1
	Malnutrition	0	1	0	0	1
Neoplasms*	Hodgkin's disease	0	1	0	0	1
Psychiatric disorders	Anxiety	0	0	0	1	1
Respiratory disorders	Lung disorder	0	0	1	0	1
Skin and subcutaneous tissue disorders	Alopecia	0	0	1	0	1
	Neutrophilic panniculitis	0	0	1	0	1

Vascular disorders	Hypotension	0	1	0	0	1
Total		3	11	24	10	48

Footnotes: *For transparency, the company are aware that one patient commenced compassionate use leniolisib with a pre-existing diagnosis of B-cell lymphoma, this patient is not referred to in the above table.
Source: Pharming Data on File, 2024.[96]

Post-marketing experience in the US

Please see Section 20.2 of the Periodic Safety Update Report / Periodic Benefit-Risk Evaluation Report in the reference pack for cumulative and interval summary tabulations of serious and non-serious adverse drug reactions sorted by MedDRA SOC in alphabetic order, then PT alphabetically, from post-marketing sources in the US ([redacted]).[97]

Conclusion

In summary, people with APDS treated with leniolisib are not expected to experience the same toxicities and adverse events as people treated with PI3K inhibitors for oncology indications. This view is shared by the experts treating APDS,[78] who concluded that, due to the distinct mechanism of action of leniolisib compared to other PI3K inhibitors, significant differences in safety profiles are anticipated. Furthermore, toxicities observed in studies of PI3K inhibitors for oncology have either not been observed during leniolisib treatment (such as opportunistic infections) or have occurred in limited number and severity (such as elevation of hepatic enzymes).

A14. Priority question: Please could you provide further details on the patients with serious adverse effects:

a) A patient who developed Hodgkin's lymphoma (Company submission, document B, section B.2.10.5). In a larger sample of patients receiving leniolisib in routine practice, is there a biologically or clinically plausible risk that some may experience Hodgkin's lymphoma as a consequence of treatment?

In a larger sample of individuals receiving leniolisib in routine practice, the company anticipate that the likelihood of developing Hodgkin's lymphoma due to leniolisib treatment is low, and no cases have been observed to date with over 300 patient-years of exposure.[98]

The case of classical Hodgkin's lymphoma in Study 2201E1 referenced above was reported at Day 750 of Study 2201E1 (DCO: 13th March 2023); this AE was not considered to be related to leniolisib by the investigator.[33] Three independent clinical assessment reports from clinical experts supported that the onset of Hodgkin's lymphoma in this participant was unrelated to leniolisib treatment:[99-101]

Professor Zinzani (Head of Lymphoma Group, Lymphoma and Chronic Lymphoproliferative Syndromes Unit, University of Bologna)	*"Globally I treated more than 150 patients with PI3Ks [inhibitors] and I [have] never seen any kind of second malignancy such as Hodgkin lymphoma in these treated patients…among several presentations at the most important national and international meetings, and in the final publications of these trials (hundred and hundreds of patients globally) we never observed cases of developing malignancies such as Hodgkin['s] lymphoma. On the basis of these data, it is*

	reasonable to think that the onset of Hodgkin['s] lymphoma is unrelated with leniolisib."
Dr Conti (Researcher and Medical Director of Paediatrics Unit IRCCS University Hospital of Bologna)	*"It would be not reasonable to attribute the development of Hodgkin's lymphoma to the employment of leniolisib; so, I agree with the previous investigator that provided the causality assessment as not related."*
Dr Sabattini (Professor, Department of Medical and Surgical Sciences, University of Bologna)	*"I tend to favour the inborn error immunity disease as the major potential cause of the development of CHL [classic type Hodgkin's lymphoma], which is likely unrelated to the drug administration."*

As described by each of the clinical experts, malignancy is one of the most frequent manifestations in APDS. In the ESID registry, by the age of 20 years the cumulative risk of malignancy is estimated to be 17% of individuals with APDS, and 43% by the age of 40 years (November 2023 dataset).[14]

Across the clinical trials and EAP, no other new malignancies were reported in the clinical trial programme and one new event of lymphoma was reported in the EAP (unrelated to leniolisib; please refer to Table 23 in the Appendix for further detail).[57] In addition, a case of lymphoma was diagnosed approximately two months after Joenja® treatment was initiated, in a case in the US; the lymphoma was deemed unrelated to leniolisib.[5]

More specifically, there has been no recurrence of lymphoma in the three participants in Study 2201 Part I with a history of lymphoma, with over six years of exposure to leniolisib.[33] Accordingly, in the EAP survey, three individuals with APDS had lymphoma prior to starting leniolisib (28/30 physician responses were captured for prior lymphoma) and none have since recurred.[43]

Considering the data presented above, the company believes the likelihood of individuals with APDS developing Hodgkin's lymphoma due to leniolisib treatment in routine practice is low. Further detail regarding the individuals who developed lymphoma after treatment with leniolisib can be found in Table 23 in the Appendix.

b) A patient who experienced cardiac arrest, and death a day later. In a larger sample of patients receiving leniolisib in routine practice, is there a biologically or clinically plausible risk that some may experience serious cardiac-related adverse effects as a consequence of treatment

Unlike other PI3K isoforms (α, β and γ), which are expressed throughout the cardiovascular system, PI3Kδ expression is largely restricted to leukocytes.[102] As leniolisib is a selective PI3Kδ inhibitor (biochemical IC50s of 240, 424, 11 and 2230 nM at PI3Kα, PI3Kβ, PI3Kδ and PI3Kγ, respectively),[103] the risk of serious cardiac-related adverse events as a consequence of leniolisib treatment is low. This is supported by available data from healthy volunteers and patients with APDS, which are outlined below.

Leniolisib and ECG findings in healthy volunteers

Study 2101 is the first-in-human study where the pharmacokinetics and pharmacodynamics of leniolisib were initially investigated.[104] The effects of leniolisib on correct QT (QTc) prolongation have been investigated in healthy volunteers, using a dataset containing 4617 electrocardiogram (ECG) assessments with time-matched leniolisib concentrations from 188 subjects enrolled in

Study 2101. This analysis found no QTc prolongation with increasing leniolisib concentration – over the range of concentrations the 90% CI upper bound of ΔQTc was estimated to be <-3 ms, well below a 10 ms threshold. Leniolisib was shown to not demonstrate a clinically meaningful QTc prolongation effect.[105]

Adverse events in the System Organ Class (SOC) 'cardiac disorders' in healthy volunteers

In Study 2101, which enrolled 188 healthy volunteers, one adverse event in the SOC 'cardiac disorders' was reported. [105]This subject was participating in the multiple ascending dose part of Study 2101. On the third day of treatment with leniolisib 70 mg bid, the participant experienced cold sweat, and rapid heart rate at 220 bpm with some chest discomfort. The diagnosis of atrio-ventricular re-entrant tachycardia and a concealed lateral bypass tract (pre-existing but undiagnosed conditions) were confirmed on electrophysiological testing. In hospital, the presence of a viral illness was noted, which on questioning had started before start of participation in the study and might have triggered the supraventricular tachycardia (SVT). While leniolisib cannot be entirely ruled-out as a contributing factor for the initiation of the SVT, other factors including the onset of a concurrent acute viral syndrome were considered to be more likely initiating causes. The final causality assessment was deemed as unlikely related to leniolisib treatment.[5, 105]

Leniolisib and ECG findings in individuals with APDS

In Study 2201 Part II, no meaningful trend was observed in ECG intervals. No participant had QTcF (corrected QT interval by Fredericia) values >500 msec, and none showed an increase of QTcF >60 msec from baseline values. The mean QTF values for the leniolisib and placebo groups at screening in Study 2201 Part II were 403.5 msec and 412.8 msec respectively. Concentration steady state should be achieved about Day 3 and the mean QTF values for the leniolisib and placebo groups at Day 15 in Study 2201 Part II were 410.6 msec and 415.6 msec, respectively. The mean QTF values for the leniolisib and placebo groups at Day 85 in Study 2201 Part II were 413.0 msec and 413.6 msec, respectively. The mean QTF values were lower in the leniolisib group than the placebo group at all time points for PK assessments and ranged from 0.1 msec pre-dose to 12 msec at 3 hours post-dose. For further detail, please refer to clinical study report for Study 2201 Part II (Table 14.3-4.1b).[5, 36]

Adverse events in SOC 'Cardiac disorders' in individuals with APDS

In Study 2201 Part II, two AEs of sinus tachycardia and tachycardia (both non-serious and asymptomatic) were observed (SOC cardiac disorders) in the leniolisib 70 mg BID group; no events were reported in the placebo group.[36]

In Study 2201E1, one cardiac arrest was reported up to the data cut-off of 13th March 2023; this event was considered not related to study treatment by the investigator. This male participant was 22 years old at the time of enrollment in the study at the US National Institutes of Health. The participant received leniolisib in Study 2201 Part II and continued treatment in Study 2201E1, with treatment ending on Day 878 after significant elevation of liver function tests (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase). Death from cardiac arrest occurred on Day 879, two days after discontinuation of leniolisib treatment. The participant had a long and protracted medical history of failure to thrive, metabolic and nutritional disorders, QT prolongation, tachycardia, cardiomyopathy, pericardial effusion, chronic mastoiditis, parotitis, chronic otitis media, recurrent/chronic pneumonia, aspiration pneumonia, chronic bronchitis, bronchiectasis, chronic necrotizing histiocytic lymphadenitis, lymphadenopathy, splenomegaly, chronic cytopenia, chronic fever, chronic norovirus enterocolitis with protein wasting enteropathy, chronic disseminated mycoplasma orale,

hypotension, chronic tachycardia, and chronic elevation of liver function tests. The participants' ECG at screening showed a HR of 58 and QTF of 432 msec. During the course of Study 2201 Part II and Study 2201E1 the participant had two ECG readings of QTF between 450-480 msec at Study 2201 Part II (Day 57) and Study 2201E1 (Days 57 and 733). No QTF value during participation in the studies exceeded 480 msec. The participant's death from cardiac arrest was attributed to the multiple medical issues the patient was experiencing, including a worsening of the chronic disseminated *mycoplasma orale* infection and underlying cardiomyopathy. The investigator found no relationship of study drug with this serious adverse event. The participant had no clinically significant ECG findings while on leniolisib either during Study 2201 Part II or during Study 2201E1. The participant was autopsied at the US National Institute of Health and the autopsy findings were consistent with the investigator's opinion.[5, 36]

Section B: Clarification on cost-effectiveness data

Systematic Literature Review

B1. In systematic reviews it is standard practice to use validated and, if possible, published search strategies as these are tested for their sensitivity and specificity in retrieving relevant records. Could the company report the source (publication or organisation) from where the search strategies for cost-effectiveness (reported in Appendix G – Published cost-effectiveness studies pg. 156) and health related quality of life (reported in Appendix H – Health-related quality-of-life studies pg. 172) have been taken? If no published source was used, could the company provide information on how those filters were created (e.g. taken from previous studies or designed by expert information specialist)?

The cost-effectiveness filter was developed based on the economic studies filter used by the Scottish Intercollegiate Guidelines Network – SIGN (which is an adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination at the University of York).[106] (To note, Lines 3 to 17 of the SIGN MEDLINE filter "Cost Allocation/ or Cost-Benefit Analysis/ or Cost Control/ or Cost Savings/ or Cost of Illness/ or Cost Sharing/ or "Deductibles and Coinsurance"/ or Medical Savings Accounts/ or Health Care Costs/ or Direct Service Costs/ or Drug Costs/ or Employer Health Costs/ or Hospital Costs/ or Health Expenditures/ or Capital Expenditures/" are all picked up by the exploding the heading: "exp Costs and Cost Analysis"/). This basis was then expanded on with additional subject headings and free text terms based on the SIGN and CADTH[107] filters, to be more sensitive and inclusive of costs and resource use.

The health-related quality of life filter was developed by a specialist systematic review team over time (through completion of numerous SLRs), using other SLRs and NICE guideline search strategy examples for both the subject headings and free text terms. Free text terms were kept broad to be sensitive, such as using generic terms (such as quality of life or utilit*) as well as scale-specific terms (such as EQ-5D). The terms used complement those used in the filters published by Sheffield Centre for Health and Related Research (ScHARR) and York Health Economics Consortium (YHEC).[108, 109]

Validatory targeted searches performed during a critical appraisal of the original search strategy did not identify any relevant studies not captured in the original SLR database searches, indicating that the search terms were sensitive.

Finally, broad disease area search terms were used for the SLRs and updates presented in the CS, to ensure sensitivity of the search strategy and minimise the risk of missing relevant publications. The disease area terms used were more comprehensive than those described by Jamee et al. 2019 (the only publication reporting search terms for a SLR in APDS).

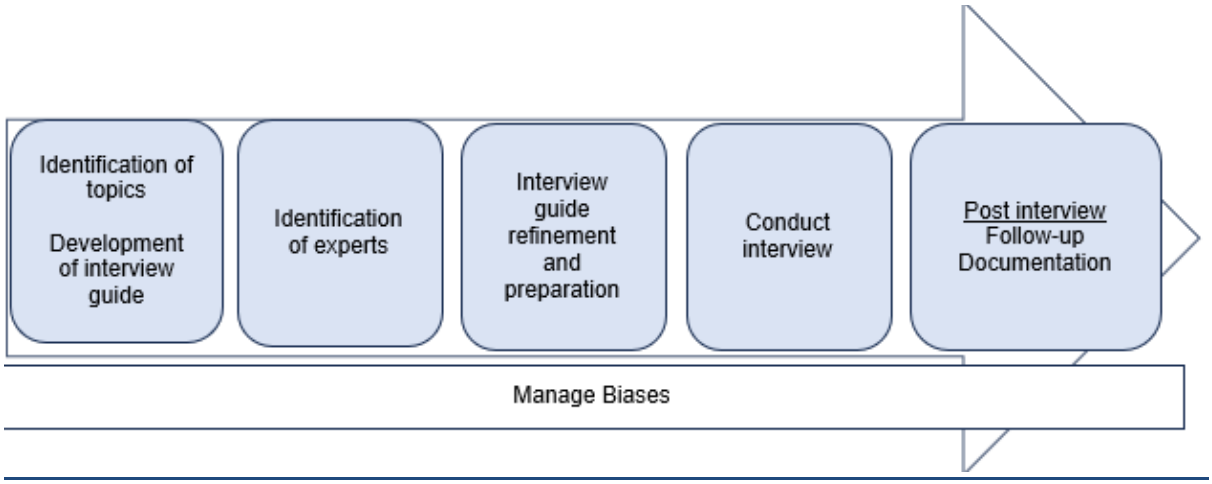
Model structure

B2. In the justification for the model structure, the company stated the model "underwent conceptual validation" by HTA experts and UK clinical expert. Could the company provide full details of the elicitation process? Could the company also provide details about the clinical validation process?

Elicitation process for conceptual and clinical validation

Virtual, semi-structured interviews were conducted to validate assumptions regarding the main characteristics of APDS, as well as how leniolisib is expected to alter the disease course and outcomes. The elicitation process is summarised in Figure 8.

Figure 8. Elicitation Process



Identification of topics

The following topics were identified as relevant for the concept validation interviews:

- Generalisability of the trial results
- Expected impact of leniolisib on manifestations, and interactions between treatments and mortality
- Potential modelling approaches/assumptions
- Guidance for further research
- A semi-structured interview guide was developed covering the aforementioned topics.

Identification of experts

The interview included 3 HTA experts (representing UK and Canada) and 1 clinical expert who is a consultant clinical immunologist (representing UK).

Interview guide refinement

The draft interview guide was piloted within the internal Pharming medical team, focusing on appropriate clinical representation of the disease process, as well as clarity of the questions posed. The interview questions were refined based on the feedback received from this internal review.

Conduct interviews

Semi-structured virtual interviews were conducted via MS Teams platform. Each interview lasted 60 minutes.

Post-interview

Follow-up questions were communicated to the experts via email. Interview reports were then prepared based on the conducted interviews and responses to follow up questions.

Clinical validation process

One UK clinical expert participated in a virtual semi-structured interview which lasted 60 minutes. The elicitation process has been described above. Information on following topics were obtained from the clinical expert:

Model structure considerations

The expert concurred with the disease considerations on age-related variability and overlap in manifestations/treatments (see Document B, Section B.3.2.2). The expert agreed on not differentiating between APDS1 and APDS2 patients, and modelling the APDS patient population as a whole.

Mortality

The expert noted modelling the APDS-specific mortality estimates rather than manifestation-specific would be more accepted by HTA agencies as it captures true outcomes for patients under current treatment. The expert further added that modelling manifestation-specific mortality would raise questions about how to combine the mortality impact of each manifestation. Therefore, the base case model captured the impact of leniolisib on overall survival, rather than modelling manifestation-specific mortality.

Impact of leniolisib on manifestations/treatments

The clinical expert agreed on the anticipated impact of leniolisib reducing gastrointestinal symptoms, and noted that a reduction in antibiotic use with leniolisib treatment could further alleviate these gastrointestinal symptoms (due to the impact of antibiotics on the gut microbiome). The expert also supported assumptions of reduced spleen surgery rate, steroid use and immunosuppressant use with leniolisib treatment, and suggested a decrease in antibiotic and antiviral use. Additionally, the expert proposed assuming fewer new cases and slower progression of bronchiectasis, as well as a reduced rate of lymphoma.

However, the expert did not agree with modelling an assumption of improvements in neurodevelopmental delays with leniolisib treatment, due to insufficient data and the multifaceted nature of these problems. Consequently, neurodevelopmental delays were not included in the final model structure.

HSCT

Regarding the impact of leniolisib on HSCT usage, the expert stated that leniolisib would reduce

the need for transplant. The final model structure therefore assumed that leniolisib will be prescribed following diagnosis, for the treatment of individuals with APDS aged 12 years or older [redacted], and assumed reduced need for HSCT.

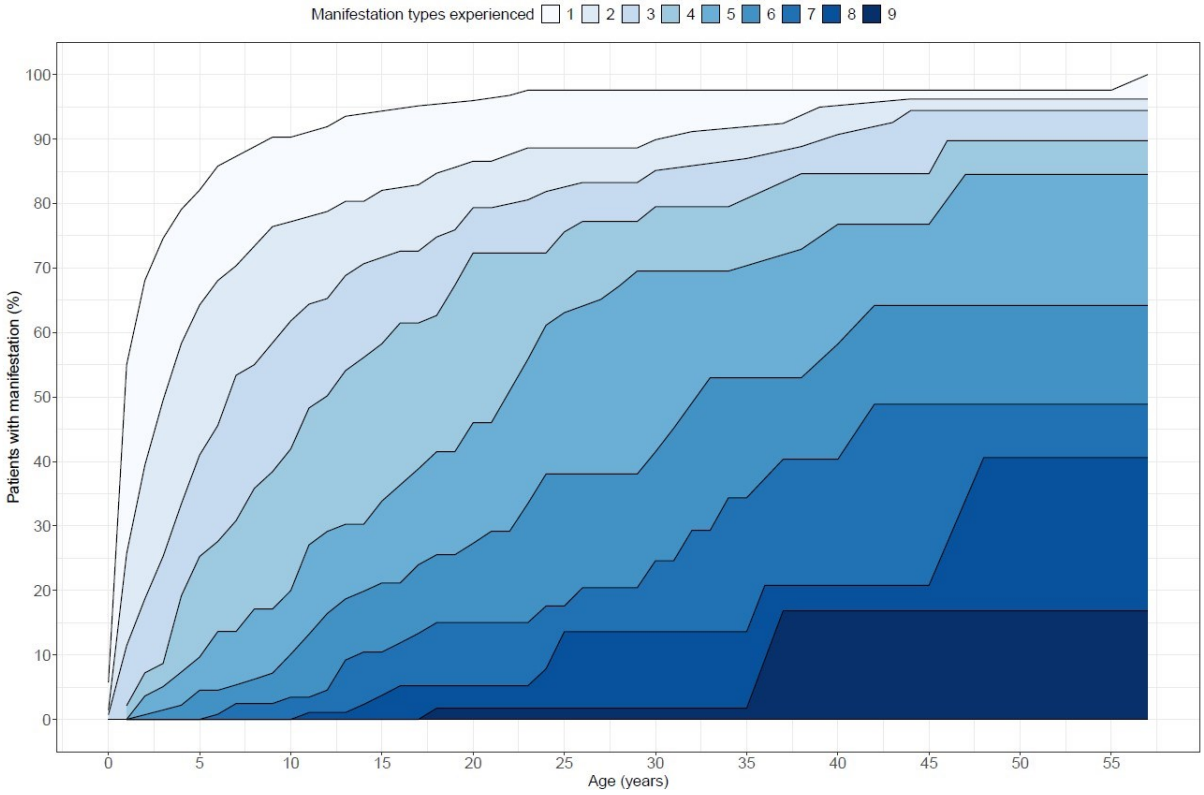
B3. Priority question: The company states that "With clinical trial data available for up to six years, there is no evidence of treatment waning, so the benefits of leniolisib are expected to be sustained lifelong" This assumption was incorporated into the economic model. However, our clinical experts have stated that although the PI3Kδ is dynamically regulated, leniolisib is not dynamic which means that how treatment effectiveness wanes over time is uncertain. Given the lack of long term evidence can the company please clarify if and why this assumption was not tested in the one way sensitivity analysis?

To date, [redacted],[95, 97] and aside from poor compliance or discontinuation (in a minority of patients) there is no clinical rationale to expect loss of effect.

PI3Kδ is dynamically regulated over hours and days with its role in the adaptive immune system, but is consistently hyperactive in APDS due to a genetic variant;[10, 35, 89] this is a lifelong condition.

- In healthy people, PI3Kδ is dynamically regulated and normal immune function requires regular activation and deactivation of the pathway.[12, 110-112] This dynamic regulation occurs over hours and days in response to stimuli, rather than a being a long-term cycle measured in years. For example, in response to antigens such as vaccination, B cells are activated and clonal expansion may peak within one week before falling back to normal levels within two weeks.[113] This process continues throughout life, as part of the adaptive immune system.
- APDS is caused by a germline variant that interferes with this dynamic regulation, resulting in consistent activation of PI3Kδ.[89] Importantly, there is no other mechanism causing APDS, hence the study of multiple PI3Kδ inhibitors for treatment of the condition, and the impossibility of another pathway causing the disease to continue (as would be expected in an oncology indication, where tumours can leverage alternate pathways to continue growth). There is also no evidence that APDS naturally resolves or becomes less severe long-term; observational data clearly demonstrate that patients continue to experience PI3Kδ hyperactivity, accumulation of symptoms and manifestations (Figure 9**Error! Not a valid bookmark self-reference.**), and life expectancy is reduced.[14, 23]

Figure 9. Number of manifestations experienced with age for individuals with APDS in the ESID registry cohort (November 2023 dataset)[a]



Footnote: [a]Manifestation types included respiratory infections, non-respiratory bacterial infections, acute viral infections, chronic viral infections, other infections, antibody-mediated autoimmunity, gastrointestinal disease, lymphoproliferation, malignancy and chronic lung disease. Individuals with missing data were not removed.
Source: Pharming Data on File, 2023.[14]

Leniolisib has a well-characterised effect of reducing PI3Kδ pathway activity without completely inhibiting the pathway.[89] This is observed in the two immediate downstream signaling pathways: reduced PI3Kδ leads to reduction in AKT and mTOR activity (reducing lymphoproliferation), while re-enabling FOXO activity (allowing class-switch recombination, which is the process by which high-affinity antibodies like IgG are created; the suppression of FOXO in APDS necessitates IgG supplementation in 60–70% of patients, as described in Document B, Section B.1.4.3 of the CS). Rao et al., 2017 demonstrated these changes *in vitro* with T cells from healthy people and those with APDS, showing reduction of pAKT and pS6 levels down to healthy levels.[2] This activity is consistent for as long as individuals are on therapy as, being a small molecule kinase inhibitor, people with APDS are unlikely to develop antibodies to leniolisib.

- The unique structure and binding properties of leniolisib provide a lower affinity for PI3Kδ than other inhibitors in the class, which results in reduced PI3Kδ pathway hyperactivation without over-inhibiting activity.[89] In preclinical study, in vitro leniolisib reduced pAKT and S6 levels to comparable levels as healthy controls in peripheral blood mononuclear cells.[2]
- In practice, this normalisation of PI3Kδ leads to restored immune function, which should be maintained as long as PI3Kδ homeostasis is present. In a six-patient cohort with six years of follow-up, patients experienced significant decreases in infection rate, prescription medicine use and specialist visits, and no progression of APDS manifestations such as lymphoproliferation or lung disease; furthermore, leniolisib was well-tolerated with only one serious adverse event (unrelated to therapy).[31] [redacted],[95, 97] over 236

years of efficacy follow-up (as of 17th May 2024).[5] The only patients who experienced a recurrence of symptoms were those who discontinued treatment in between Study 2201 Part I and the Study 2201E1. During the treatment-free period between completion of Part I and enrolment in Study 2201E1, the six patients had an average treatment gap of 233 days (range: 136 to 556 days); over this time, four of the six patients reported an increase in activity impairment due to health (with no change in the remaining two).[33, 36] While imaging was not undertaken as part of the protocol, data from one patient showed a >200% increase in spleen volume during a 15-month gap.[114] In addition, IgM values all increased rapidly, indicating a rapid loss of ability to develop IgG.[33, 36]

- Further evidence of sustained pathway normalisation comes from patterns of long-term IRT use. While changes to IRT regimens were not protocolised in Study 2201, physicians have reduced or stopped IRT dosing in 37% of patients, (with 15% of patients stopping IRT).[31] In Study 2201 Part I, 5 of the 6 participants enrolled were treated with IRT; the treating physicians subsequently discontinued therapy for two patients and reduced IRT dose for two more, but these patients have maintained normal IgG levels through six years of follow-up. (Note that the Study 2201 protocol mandated serum immunoglobulin testing up to Day 252, but the investigators chose to continue testing serum immunoglobulins for the six patients in Study 2201 Part I, and published their results outside of the CSR.).[2, 31]

With no loss of efficacy observed while on therapy, no alternative signaling pathway for APDS progression and no obvious mechanism for development of leniolisib resistance, the only remaining means of lost effect are discontinuation or poor adherence.

- Discontinuation is already captured in the company's economic evaluation (Document B, Section B.3.3.6 of the CS).
- Participants demonstrated high treatment adherence in Study 2201, as measured by pill count at each visit. Total exposure in the Extension phase was a mean of 155,674.3 mg over 159.76 weeks (Table 14.1-4.1).[33]. At a dose of 70 mg bid, the expected total consumption would have been 156,564.8 mg, indicating 99% compliance.
- In the US, where Joenja® became commercially available in March 2023, people treated with leniolisib have also been highly adherent. From Q2 2023 (first quarter after March 2023 launch) through Q1 2024, among 100 patients who have started treatment, the average number of "gap days" (defined as a day without medication) was just 2.6.

In the long term, high adherence rates are expected with leniolisib, as lymphoproliferation and other symptoms may rapidly return for people who are less compliant. In this situation (which would suggest lack of efficacy), a patient would either improve compliance or an HCP would look to return to symptomatic management. Therefore, one potential way of modelling poor compliance would be an increase in the discontinuation rate. The CS included a scenario with a hypothetical annual discontinuation rate of 14% (approximately five times the base case discontinuation rate), in which the ICER was £[redacted] QALY gained (see Document B, Section B.3.10.3 of the CS; QALY weighting was not applicable to this scenario based on the incremental QALYs). This ICER is similar to the base case ICER of £[redacted]/QALY gained.

Clinical parameters and variables

B4. Priority question: In their summary of the cost-effectiveness analysis (Section B.3), the company states that a 1.5% discount rate for the future

health effects was used in their base-case analysis, which the EAG believes is inconsistent with NICE guidance, in which a 3.5% discount is recommended. NICE states that there are some exceptions when alternative discount rates are acceptable (all criteria need to be met): 1) The technology is for people who would otherwise die or have a very severely impaired life; 2) It is likely to restore them to full or near-full health; 3) The benefits are likely to be sustained over a very long period.{NICE, 2022 #3}

Given the NICE criteria mentioned above, could the company clarify how the above criteria are met for this HST and therefore provide further justification regarding the use of a 1.5% health effects discount rate? If the company is unable to meet the NICE criteria of using this alternative discount rate, could they conduct the base-case analysis applying the 3.5% discount rate?

The company believes that a discount rate of 1.5% per annum for health effects is appropriate for the economic analysis of leniolisib in APDS, given that all three criteria are met by the technology as justified in Table 15.

Table 15. Justification for the use of a discount rare of 1.5% per annnum for health effects in the base-case analysis

Criterion 1: The technology is for people who would otherwise die or have a very severely impaired life	Individuals with APDS can experience severe and often persistent manifestations from early in life and throughout their lifetime, which have a substantial negative impact on HRQoL[10, 44, 115, 116] and shorten life expectancy.[23, 117] During the pre-submission stages for this evaluation, NICE acknowledged that leniolisib met HST criterion 3, with the TSOP panel stating that it is reasonable to conclude that APDS reduces the quality and length of life. **Leniolisib is for people who would otherwise die** Despite currently available treatments, published case studies of cohorts with APDS demonstrate that one in four individuals do not survive into early adulthood.[11, 23, 118, 119] The most recent and comprehensive case series providing mortality data for APDS, indicates that among 351 individuals, 41 (11.7%) deaths had occurred. The estimated probability of survival drops to just 25% by 65 years of age; the average age at the time of death was 19.6 years.[117] As this study searched for all reported cases of APDS to inform a case series and survival analysis, publication bias and underreporting of poor outcomes in the literature is likely to have led to this study underestimating mortality in APDS. Supplementary analyses of the ESID registry further support this high mortality rate, where 50% of individuals experienced either malignancy or death by age 40, rising to 73% by age 57, the highest

	age for which data were available.[14] Lymphoma is the dominant cause of death, responsible for 24–42% of all fatalities, with the median age of malignancy diagnosis being 19 years.[10, 23, 45, 120] Non-malignant causes of early mortality include severe respiratory infections, chronic lung infections, intestinal perforation, respiratory failure, cardiopulmonary arrest, bowel perforation, septic shock, multiple organ failure following HSCT, and pulmonary haemorrhage.[9-11, 35, 120] Given the recent recognition of APDS as a unique condition and the corresponding availability of diagnostic testing,[121] it is likely that these data highly underestimate mortality in this population, as they do not account for deaths where a definitive diagnosis of APDS was not established.[5] Without leniolisib treatment, people with APDS are likely to experience a severely reduced life expectancy and high mortality risk. Through engagement with over 25 immunology departments in England over the past 2.5 years, the company is aware that multiple individuals with APDS in England have died prematurely due to consequences of the disease. It is also accepted that rate of malignant transformation of APDS is likely to be an underestimate as people with APDS presenting with lymphoma in the early course of disease are not routinely investigated for IEI as a cause of disease.[5] **Leniolisib is for people who would otherwise have a very severely impaired life** The onset of APDS occurs very early in life; recent analyses of the ESID registry by Thalhammer et al., 2021 and Maccari et al., 2023 found that 36% of the APDS cohort presented with manifestations in the first year of life, >70% in between ages 1–5, and >90% in between the ages of 6–10 (n=122; March 2019 dataset). The median age at first clinical manifestation was 1 year (n=170, November 2022 dataset).[10, 122] People with APDS can experience several manifestations simultaneously; the associated symptoms can have cumulative negative impacts on HRQoL.[10, 44, 115, 116] The increased risk of malignancy with APDS from early in life,[9-11, 123] and irreversible end-organ damage such as advanced lung disease and/or hearing loss, have notable impacts on patient HRQoL.[6, 8, 44, 45] A recent analysis of the APDS cohort in the ESID registry found that the median age for individuals with APDS experiencing 3 manifestations was seven years, with six manifestations experienced by age 33 years. By adolescence the majority of individuals with APDS will experience multiple life-limiting manifestations.[14] In Exercise 2 of the Expert Consultancy, clinical experts completed the EQ-5D questionnaire based on various vignettes. The resulting utility values indicate that clinicians perceive that people with APDS experience substantial HRQoL burden. The highest utility value for

	individuals with 5 manifestations was 0.412, whereas the utility value for individuals with 8 manifestations was only –0.014 (utility values are the highest utility value amongst individuals with 5 or 8 manifestations).[74] Each clinical manifestation of APDS is also associated with substantial negative impacts on patient HRQoL, which are further described in Document B, Section B.1.4.2 and summarised below: • Lymphoproliferation can lead to lymphadenopathy, which can result in painful and large lymph node swellings across the body (including tonsils and lymph nodes in the chest) and difficulty breathing.[46, 73-75] Moreover, swollen tonsils and/or adenoids can impact the ability to sleep and eat, with gagging and difficulty swallowing reported.[46] • Individuals with APDS with gastrointestinal manifestations can experience disabling and frequent symptoms,[46, 124] including struggling with their diet and maintaining weight, stomach pains, requiring a gastronomy tube (G-Tube) for nutrition, as well as chronic diarrhoea, all of which impacts their sleep and daily activities, including work.[46, 74, 125, 126] • Autoimmune cytopenias can have negative impacts on energy levels, and can lead to episodes of dizziness, breathlessness whilst carrying out daily activities, as well as an increased risk of bleeding and bruising compared to healthy individuals without APDS.[74, 127-130] • Individuals with lymphoma experience significant psychological distress and impaired HRQoL, including constant anxiety about the occurrence/recurrence of lymphoma, fear of poor response to treatment, social isolation, panic, suffering and death.[74, 131] • Individuals with APDS frequently experience recurrent oto-sinopulmonary infections, presenting with persistent cough, sore throat, high fever, muscle aches and chest pain, severely impacting their HRQoL and ability to carry out their daily activities.[7, 46, 74, 125, 132, 133] • Lung disease can cause individuals with APDS to struggle with their breathing, experience chest pain and need supplementary pulmonary support. Lung disease can also lead to sleep apnoea, negatively impact energy levels and lead to feelings of frustration.[28, 29, 46, 74, 134, 135] In addition to the high symptom burden, individuals endure intensive treatment regimens with frequent and prolonged hospital visits with invasive treatments.[9, 10, 118, 136-138] Ultimately, these current treatments do not target the root cause of APDS therefore, individuals with APDS continue to experience disease progression and potentially life-threatening manifestations, resulting in a reduced quality of life and life expectancy compared with people without APDS.[9-11, 35, 118] Moreover, these treatments can come with frequent

and severe side effects, invasive administration methods, and lifelong adverse impacts.[6, 137-141]

QALY shortfalls

The company acknowledges that QALY shortfall calculations are considered for the application of severity modifiers for technologies being evaluated via the (standard) technology appraisal route, rather than HST evaluations. However, in order to provide quantitative evidence in keeping with an existing NICE framework to demonstrate the life-limiting nature and severity of APDS, the company has provided QALY shortfalls below. Based on the inputs shown in Table 16 and Table 17, leniolisib would be eligible for the highest severity weight of 1.7 (Table 17). Therefore, this QALY shortfall analysis demonstrates that APDS falls within what NICE considers severe in terms of future health lost compared to people without the condition. It is therefore reasonable to conclude, based on this NICE framework, that criterion 1 for the use of a 1.5% annual discount rate can be considered met.

Table 16: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Justification
Sex distribution	49% female	ESID registry APDS cohort, November 2023 dataset
Starting age	15 years	Average age of people with APDS in the Level 1 (mandatory) dataset of the ESID registry (November 2023 dataset) and in alignment with the economic analysis
Discounting rate	0%	To demonstrate the full QALY shortfall and impact of discounting

Abbreviations: APDS: activated PI3K delta syndrome, ESID: European Society for Immunodeficiencies.

Table 17: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
57.29	14.42 (total undiscounted QALYs derived from the current clinical management arm of the economic	• Absolute QALY shortfall: 42.87 • Proportional QALY shortfall: 74.83% • QALY weight (as per

	<table><tr><td></td><td>analysis, with no discounting applied)</td><td>STA guidance): 1.7x</td></tr></table> **Abbreviations:** QALY: quality-adjusted life year; STA: standard technology appraisal. **Source**: Schneider et al., 2021.[142]
Criterion 2: It is likely to restore them to full or near-full health	Leniolisib targets the underlying pathophysiology of APDS, normalising immune cell subset levels to normal reference ranges, leading to improved immune system functioning. The clinical data presented below demonstrates that leniolisib is able to resolve manifestations in substantial proportions of individuals. As such, leniolisib is likely to restore full or near-full health in individuals with APDS, providing substantial and sustained benefits for both their quality and length of life. **Improvements in immune dysregulation measures** Lymphoproliferation is a hallmark characteristic of APDS, and was observed in 86% of individuals with APDS in the ESID registry cohort (146/170; November 2022 dataset).[10] Upon examining the number of affected individuals in the EAP survey (described in Document B, Section B.2.4.2), for the people experiencing lymphoproliferation prior to the initiation of leniolisib, **clinically meaningful improvements were observed in 75% of people**, with remission by achieved by 21% of individuals.[29] The reductions from baseline in lymphadenopathy (SPD in index lesions) in the clinical trials were **associated with improvements in patient HRQoL**, where a decrease in the SPD was significantly associated with CfB to Day 85 in PtGA (p=0.034).[58] Supplementing these exploration analyses, clinical opinion indicates that individuals experiencing improvement in lymphoproliferation will no longer experience the HRQoL impact associated with lymphoproliferation.[6] Additionally, during the validation of the modified SEE results, a clinical expert highlighted that improvement in lymphoproliferation as seen with leniolisib treatment could be regarded as symptomatic resolution, consequently mitigating any further impact on HRQoL.[6] The available evidence shows that leniolisib treatment reduces the incidence or resolves swollen lymph nodes across the body and therefore has the capacity to restore individuals to near-full or full health, respectively, as well as improve patient HRQoL. Upon examining the number of affected individuals in the EAP survey, considering people with APDS presenting with gastrointestinal manifestations prior to initiation of leniolisib, **remission was achieved in 36% of participants experiencing gastrointestinal manifestations**. In addition, clinically meaningful improvements were observed in a further 50% of people with APDS receiving leniolisib. Therefore, leniolisib treatment led to clinically meaningful improvement or remission of gastrointestinal manifestations in a large proportion (86%) individuals with APDS in the EAP survey.[29] This suggests that leniolisib can restore

	individuals to near-full or full health, substantially improving patient HRQoL and allowing them to return to a more normal life. Through to Week 36 of Study 2201E1, **78% of participants treated with leniolisib achieved a clinically meaningful response** in the combined responder analyses for cytopenias. A clinically meaningful response was defined via a Delphi panel as a median increase of ≥20% in haemoglobin levels, as well as platelet and lymphocyte counts, after three months of treatment (discussed in Document B, Section B.2.4.2). Notably, the Study 2201E1 data indicated no signs of rescue medication, with the majority of participants reaching normal levels of platelets.[32, 33] Therefore, it was concluded that all patients whose cytopenia responded to leniolisib treatment (per the Delphi panel responder thresholds) experienced resolution of cytopenia with regards to its HRQoL impact. This may lead to increased energy levels, capacity to exercise and perform daily tasks, as well as a reduced risk of bleeding and bruising.[127-129, 143, 144] Furthermore, in the EAP survey, considering the individuals with APDS presenting with cytopenia prior to initiation of leniolisib, remission was achieved in 40% of individuals, whilst clinically meaningful improvements were observed in an additional 40% of individuals.[29] **Improvement in immune deficiency measures** In Study 2201 Part II, annualised infection rates were lower in participants treated with leniolisib compared to the placebo group (2.690 versus 3.476 infections per year). Accordingly, in Study 2201E1, 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).[33] A **nominally significant decrease in annualised infection rates** of 25% was reported with each additional year of leniolisib treatment (−0.282 infections per year, one-sided p=0.0256; DCO: 13th March 2023).[145] Reductions in the incidence of infections were accompanied by **sustained reductions in IRT use**, as well as some **individuals achieving IRT freedom** during Study 2201E1.[8, 32, 33, 145, 146] These findings indicate restoration of immune system functioning and a subsequent decreased reliance on or cessation of requiring IRT. **Lung disease** Recent analyses of the ESID registry identified that bronchiectasis was experienced by 40.0% of the known APDS population by the age of 15, and 70.0% by the age of 45 (November 2023 dataset).[14] In a case study of six study participants, of the three participants who had developed bronchiectasis prior to entering Study 2201 Part I, **bronchiectasis did not progress in any of the individuals through six years of treatment with leniolisib during Study 2201E1**.[30] As presented in clarification question A.5, lung imaging was retrospectively analysed for the participants in Study 2201 with CT images at screening, 12 weeks, and Day 168 or 252 of Study

	2201E1. For the eight participants who showed radiological evidence of bronchiectasis at screening, there was no evidence of development or progression of bronchiectasis in these 8 participants between screening and extension Day 168 of Study 2201E1; two patients (randomised to leniolisib during Study 2201 Part II) showed slight improvements in lingular bronchi (including improvement in bronchial wall thickening).[147] In addition, in the longer-term Study 2201E1, there were **no new cases of infective exacerbations of bronchiectasis reported**.[33] In the EAP survey, considering the people with APDS presenting with lung disease prior to initiation of leniolisib, **remission was achieved in 29% of individuals**, whilst clinically meaningful improvements were observed in 24% of people.[29] Supplementary data from an Australian case study highlight **improved oxygen saturation** (SpO_2; 88% to 98% on room air) and **improved lung function after six months of leniolisib treatment** (spirometry FVC: increasing to 1.8 and FEV1: increasing to 1.1).[27, 28] Evidence and expert opinion suggests that leniolisib treatment prevents the progression of bronchiectasis, but is also expected to reduce the risk of long-term organ damage caused by chronic inflammation,[6, 46, 125, 132] and may have a positive impact on lung function. This in turn diminishes the need for supplementary pulmonary support enabling individuals to return to their normal lives (e.g. back to university and/or work).[28-30] **Malignancy** In Study 2201E1, as of the latest DCO (13th March 2023), a case of classical Hodgkin's lymphoma was reported which led to treatment discontinuation; this AE was not considered to be related to leniolisib, by the investigator. Although lymphoma is the most common type of malignancy in people with APDS,[10, 11] **no other new malignancies were reported in the clinical trials, including in participants with a history of lymphoma**[32] and no participants received HSCT whilst receiving leniolisib treatment.[5] In the EAP survey, three individuals with APDS had lymphoma prior to starting leniolisib (28/30 physician responses were captured for prior lymphoma) and none have since recurred.[5, 29] Considering the overall EAP, only one new case of malignancy was reported in a total of 60 individuals,[29] with 102.5 patient-years of follow-up (as of 17 May 2024); this case of malignancy was not associated with leniolisib.[5] Furthermore, there have been no cases of malignancy for patients treated with commercial supply of leniolisib in the US or abroad (using commercial supply) over approximately 60 patient-years of follow-up.[148]

	Disease severity and HRQoL The clinical improvements seen with leniolisib treatment have a positive impact on the everyday lives of people with APDS, with numerical improvements in HRQoL measures, such as SF-36 and PtGA, observed in the leniolisib clinical trials (as described in Document B, Section B.2.6.7).[33, 34, 36] Rao et al., 2024 explored the six individuals with APDS who received leniolisib for up to six years. In these individuals, **5/6 patients individuals reported an increase in physical capabilities and socialisation, and a decrease in prescribed medications**. At enrollment, 3/6 participants missed school or required homeschooling, but during the trial, these same individuals completed their high school, college, or secondary education. Additionally, 5/6 participants joined the workforce in either remote or in-person jobs.[31] These findings suggest that leniolisib helps individuals return to work and lead more normal lives, indicating a restoration to near-full or full health. Overall, the data from the clinical trials, EAP and case studies presented above demonstrate that leniolisib is able to resolve manifestations in a substantial proportion of individuals, and improve HRQoL. These findings strongly suggest that leniolisib is likely to restore individuals with APDS to near-full or full health.
Criterion 3: The benefits are likely to be sustained over a very long period	As discussed in the response to criterion 2, leniolisib directly addresses the root cause of APDS, normalising immune cell subset levels and improving immune system function. This leads to long-term benefits in both immune dysregulation (e.g. decreased lymphadenopathy) and immune deficiency (e.g. reduced frequency of infections), resulting in reduced or ceased use of supportive medications and improvements in HRQoL. These changes are expected to reduce mortality and offer substantial benefits across a range of patient-relevant endpoints. These include significant improvements in lymphadenopathy, a reduced frequency of infections and hospitalisations, and decreased reliance on treatments such as IRT. Leniolisib treatment is expected to begin early in life, starting at age 12 or upon diagnosis if later. The long-term efficacy of leniolisib is supported by over 200 patient years of exposure in the clinical trial programme and EAP.[5] Across the six years of follow-up in the leniolisib clinical trials, observed benefits have been sustained across all endpoints.[31, 33] EAP survey data based on approximately 34 patient-years of exposure also indicate that none of the pre-existing non-infectious complications worsened following the initiation of leniolisib.[5, 29] Furthermore, based on the mechanism of action of leniolisib, it not is biologically plausible to expect treatment effect waning, reinforcing the potential for sustained benefits over time (see clarification question B.3 for rationale).

	Overall, clinical evidence demonstrates that leniolisib improves outcomes for people with APDS across a range of clinically- and patient-relevant endpoints, over a substantial duration of follow up, and over a high number of patient years of exposure, underscoring the critical importance of early and sustained treatment with leniolisib.

B5. Regarding the impact of leniolisib (Section B.3.3.4), the HR estimate for survival is based on only 5 clinicians in the modified structured expert elicitation (SEE) exercise, implying there could be large uncertainty. However, the estimated standard error (SE) is only [redacted] (much smaller SE compared with the mean, i.e., [redacted]). Given that this HR value can be a key driver of the CE results in the views of EAG. Could the company provide: a) the values elicited from the clinicians that can be used to inform the SE, (b) the calculation process for the mean and SE for this HR estimate? and (c) full details of the modified SEE exercise?

During the clarification call on the 20th June 2024, the company agreed to re-share the Expert Consultancy report which includes the full details of the modified SEE exercise, including the values elicited from clinicians (see Section 3 for Exercise 1). Please refer to the included Microsoft Excel spreadsheet in the reference pack titled "*Pharming_Mortality HR Calculations from the Expert Consultancy*" for details of the calculation process. In summary:[6]

- The experts' plausible range for long-term survival after age 12 under current clinical management was used to calculate a cumulative hazard, which was then annualised, resulting in a median value of 0.0118.
- Expert commentary suggested the survival curve for leniolisib should be closer to that of the general population; therefore, each expert's upper plausible estimate for long-term survival on leniolisib treatment after age 12 was used to calculate a cumulative hazard, which was then annualised, resulting in a value of [redacted].
- Division of the annualised hazard for individuals after age 12 under current clinical management by the annualised hazard for individuals after age 12 on leniolisib resulted in a mean HR of [redacted] for long-term survival.
- The SE was assumed to be 20% of the point estimate, resulting in a value of [redacted].
- The cumulative hazard of mortality under current clinical management of 0.0118 is substantially lower than the mortality rate of 73.5% observed from age 12 to 67 in the Pharming case series data, which would indicate an annualised hazard of 0.0241. However, for consistency in the calculation and to provide a conservative estimate of survival gains for leniolisib, the expert opinion was used.

Considering the ultra-rare and complex nature of APDS and the small number of available experts with relevant experience with APDS and leniolisib, a substantial total of ten clinicians were included in the Expert Consultancy project.[6] Notably, it is acknowledged that the number of experts in Group 1 who completed both Part 1 and Part 2 of the modified SEE and the EQ-5D-5L Exercise, is one fewer than the five experts per exercise minimum recommended by the York Centre for Health Economics reference protocol for expert elicitation in health technology assessment (HTA).[149] Despite this, the pool of experts covered both adult and paediatric specialities across several National Health Service (NHS) Trusts in the UK, as well as sites in

Europe and Canada, thus enabling a broad range of clinical experiences and practices to be included.

Measurement and valuation of health outcomes

B6. The company has undertaken a targeted search for proxy utility values on conditions and manifestations to populate the economic model (Appendix O - Targeted search for proxy utility values pg. 254). Can the company provide detailed information of the databases they searched, the date of searching, the number of records retrieved by the searches and excluded at title and abstract as well as a rationale for the use of a different cost and utility related terms from the ones used and reported in the cost-effectiveness and health related quality of life literature searches undertaken and reported in Appendices G and H respectively.

Given the lack of appropriate utility data identified from the clinical trials and HRQoL/utility SLR, extensive, targeted and broad-scoped literature searches were carried out to augment the evidence base. Such broad and extensive searches were required due to the limited published data for APDS and for proxy primary immunodeficiencies. A snowballing approach was employed, and model inputs were identified through an iterative process.

Phase 1 of Targeted Searches (Initial Model Development: October 2022)

The first phase of targeted literature searches involved two steps:

- The first search focused on diseases that were similar in their clinical presentation to APDS (i.e. APDS 'proxy' diseases). CTLA-4 deficiency, LRBA deficiency, ALPS, STAT3 GOF, Hyper-IgM syndromes, and CVIDc (complex CVID/CVID with non-infectious complications) were recommended as proxy diseases by clinical experts.[150]
- As many of the proxy diseases were also ultra-rare diseases, where no reliable information was obtained from the aforementioned proxy disease focused search, the search was subsequently broadened to include manifestation/treatment specific search terms.

The proxy disease-focused searches were conducted on 11th October 2022. Open access studies reporting information on the survival, HRQoL or costs for proxy diseases were eligible for inclusion. Geographic or date limits were not applied. The search of PubMed returned 3,610 articles, and following title screening, 15 articles were selected for abstract screening. Following review, 7 articles were identified for full text review of which 5 articles were excluded, leaving 2 articles for inclusion. 3 additional articles were identified through citation searching.

As all the required data for model development were not obtained from proxy disease-specific searches, manifestation/treatment specific searches were carried out on 14th October 2022. As with the first search, open access studies reporting information on the survival, HRQoL or costs for specific manifestations were eligible for inclusion, with no geographic or date limits applied. A search of PubMed returned 12,325 articles. Most articles were excluded at the title review stage, with 39 articles selected for abstract screening. Following abstract review, 21 articles were identified for full text review, of which 11 articles were excluded, leaving 10 articles for inclusion. Two additional articles were identified through citation searching (as part of the 'snowballing' approach).

A total of 12 articles were identified during the first phase of targeted literature search (as presented in Appendix O in the company submission).

Phase 2 of Targeted Searches (Model Updates: 2023-2024)

Further *ad hoc* searches were carried out as needed to augment the information obtained from Phase 1 of the targeted searches. To ensure consistency with prior technology assessments, studies cited in previous NICE technology appraisal were given priority for selection as inputs, over some of the data identified in the Phase 1 searches.

Table 18summarises the inputs identified through the Phase 2 *ad hoc* literature searches.

Table 18. Details of ad-hoc literature search

Inputs obtained	Identified study and rationale	Dates searched
Bronchiectasis associated airway disease utility	• Brockwell et al., 2020[151] • Altenburg et al., 2013[152] was identified as the potential source of utility data in the first phase of literature searches, however it reported SGRQ values which were mapped to EQ-5D based on mapping algorithm by Sperlich et al., 2022.[153] Due to inherent uncertainty with the mapped values, Brockwell 2020 was preferred (EQ-5D-3L completed by patients).[151]	11th October 2023
Advanced lung disease utility	• Bradley et al., 2013[154] • Cystic fibrosis was identified as proxy disease based on clinical expert opinion (Expert Consultancy project)[6]	11th October 2023
Cytopenia utility	• Snyder et al., 2008[155] • Immune thrombocytopenic purpura was identified as proxy disease based on clinical expert opinion (Expert Consultancy project)[6]	11th October 2023
Gastrointestinal disorders utility	• Wilson and Lucas 2018 (utility for Crohn's disease)[156] • Inflammatory bowel disease was identified as proxy disease based on clinical expert input (Expert Consultancy project)[6]	23rd January 2024
Splenomegaly	• Mesa et al., 2021[157] • Symptoms associated with enlarged lymphoid organs in myelofibrosis patients were identified to be similar for APDS patients based on clinical expert input.[6]	23rd January 2024
HSCT disutility	• Sung 2003[158] HSCT follow-up cost was obtained from HST18 (which was based on Hettle et al. 2017 – NICE Regenerative Medicines Report).[159] • The disutility used in Hettle et al., 2017 report was used in the model for consistency.[159]	12th April 2024

The targeted searches and HRQoL/utility SLR served different purposes and were conducted at different times. The HRQoL/utility SLR took a broad and systematic approach to identifying HRQoL evidence in APDS. These terms were more structured, using a broad yet comprehensive set of disease area and utility terms including subject headings and keywords, combined in a more segmented and detailed manner and were translated for use in multiple databases. As discussed in Question B1, the search terms were developed using other SLRs and NICE guideline search strategy examples for both the subject headings and free text terms and complement ScHARR and YHEC filters.The search strategies for the targeted searches were more specific, conducted on PubMed alone, and tailored towards identifying specific data of interest at the time that the searches were conducted, based on evidence that had been found to date.

B7. The EQ-5D vignette valuation survey was mentioned in Section B.3.4.3 and in the appendix. We thank the company for the submission of the vignettes from the EQ-5D exercise. Could the company provide the full details of the development, validation and results as these have not been submitted as part of the company submission. The provided reference "Pharming Data on File. Healthcare professional valuation of health states in APDS using EQ-5D-5L. 2024" is not accessible. Could the company provide the details of this survey please?

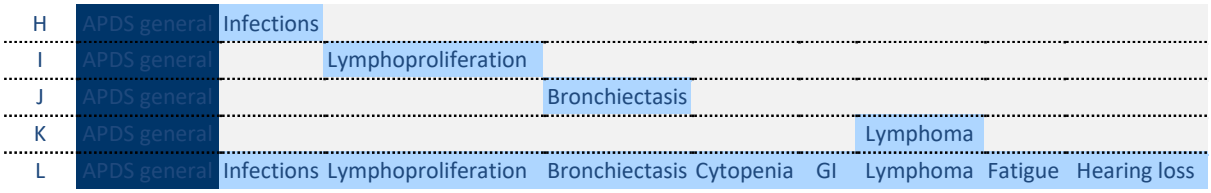
The EAG have confirmed that they are now able to access the report for the EQ-5D exercise. The company have also provided a summary of the survey below. For further details regarding the development, validation and findings, please do refer the full report titled "*Pharming_Exercise 2_EQ-5D-5L HCP Valuation_20Mar2024*".

The EQ-5D survey explored the impact of various symptoms and manifestations of APDS on patient HRQoL using a vignette-based approach to generate utility values. In total, 12 vignettes were developed based on patient interviews, existing literature, and expert validation with two UK clinical experts. Vignettes included various combinations of APDS symptoms such as infections, lymphoproliferation, bronchiectasis, autoimmune cytopenias, gastrointestinal issues, lymphoma, fatigue, and hearing loss (see Table 19).[160]

These vignettes were assessed using the EQ-5D-5L questionnaire, a preference-based measure. Due to the complex nature of ultra-rare diseases like APDS, direct patient-reported utility data was not feasible, leading to the use of proxy reports by clinical experts. The study involved four clinical experts from Italy, Spain, and the UK, who rated these vignettes using the EQ-5D-5L Proxy 1 version, designed to reflect their perceptions of patient HRQoL. The EQ-5D-5L captures HRQoL across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five response levels.[160]

Table 19. Overview of the 12 includes health state vignettes

A	APDS general	Infections	Lymphoproliferation[a]				
B	APDS general	Infections	Lymphoproliferation	Bronchiectasis			
C	APDS general	Infections	Lymphoproliferation		Cytopenia		
D	APDS general	Infections	Lymphoproliferation			GI	
E	APDS general	Infections	Lymphoproliferation	Bronchiectasis	Cytopenia	GI	
F	APDS general	Infections	Lymphoproliferation				Lymphoma
G	APDS general[b]						



Footnotes: [a]"Lymphoproliferation (including lymphadenopathy and splenomegaly)" streamlined to "lymphoproliferation" for readability. [b]Vignette G refers to the *baseline health state* for APDS and therefore, no manifestations have been included.
Abbreviations: APDS: Activated phosphoinositide 3-kinase delta; GI: gastrointestinal.
Source: Pharming Data on File., 2024.[160]

The ratings provided by the experts were converted into utility values using the UK value set algorithm (Devlin *et al.* 2018).[161] Mean utility values per health state varied from [redacted] for APDS general (*baseline health state*) to -0.109 for APDS general + infections + lymphoproliferation (including lymphadenopathy and splenomegaly) + bronchiectasis + autoimmune cytopenias (including neutropenia, anaemia, and thrombocytopenia) + GI + lymphoma + fatigue + hearing loss. The second lowest utility value was reported for the health state describing APDS general + infections + lymphoproliferation (including lymphadenopathy and splenomegaly) + lymphoma at 0.220, followed by APDS general lymphoma at 0.278. The health states describing individual manifestations generally elicited higher utility values, indicating that combination health states (involving several manifestations) were perceived to have a worse impact on patient HRQoL.[160] The company would like to note that the baseline utility for APDS in the economic analysis ([redacted]) was calculated based on the mean APDS general utility values for males and females after mapping to EQ-5D-3L (Tables 8 and 9 in the report), to align with section 4.3.16 of the NICE methods and processes guide (PMG36).[162]

Sensitivity analyses were conducted to assess and compare the outcomes of removing negative utility values and capping negative values at 0. Results were minimally affected by mapping the values to the EQ-5D-3L using the Hernandez-Alva algorithm.[163]

The results were validated with a UK clinical expert, and they overall agreed that the presence of lymphoma and experiencing multiple manifestations simultaneously substantially impacts patient HRQoL.[160]

Overall, the results demonstrated that the clinical experts perceive that patients with APDS experience substantial HRQoL burden, which is particularly apparent in patients who experience multiple manifestations simultaneously and/or develop lymphoma. These findings align with published literature which has reported that patients with chronic medical conditions, such as CVID, diabetes mellitus, and multiple sclerosis (MS), face a substantial HRQoL impact when experiencing multiple manifestations or comorbidities simultaneously.[160]

B8. The EAG understands leniolisib may have positive emotional impacts on patients. The company states that "Based on previous studies, a utility gain of 0.1 is

expected to capture the overall improvement in the wellbeing of patients associated treated with leniolisib" (Section B.3.8.2):

Could the company provide further explanation on how the value of 0.1 was derived from the literature. Please provide further details on the conditions and context of the studies informing the calculation of the treatment gain value.

In the PSA, the company assumed no uncertainty (i.e., standard error=0) for this utility value. Please provide justification of why a standard error of 0 was assumed for this utility range. Please provide a plausible range of values for the standard error to inform a one-way sensitivity analysis?

As described in Document B, Section B.3.8.2, and as acknowledged by the EAG, a utility gain of 0.1 was included in the model to capture the overall improvement in the wellbeing of patients treated with leniolisib, including increased vitality and reduced anxiety, and improvement not captured within the economic model.

Prior Studies

Previous studies reporting on the impact of a positive view of life, optimism, and an absence of anxiety on quality of life identified by the company are summarised in Table 20 and below; the company anticipates that the quality of life benefits associated with leniolisib will extend beyond these three factors (e.g. benefits associated with increased vitality). The studies included below by Hedman et al., 2018, Kung et al., 2006 and Short et al., 2021 included patients from Canada, US and Sweden,[164-166] all of which are anticipated to be relevant to the UK population.

Impact of a positive view of life and optimism on HRQoL

Positive view of life

Hedman et al., 2018 studied the impact of fear of disease recurrence and life perspective on HRQoL in 235 Swedish patients with differentiated thyroid carcinoma. The study reported that patients with a negative view of life had lower HRQoL, as measured by SF-36. Houten et al., 2021 mapped these findings to EQ-5D utilities, showing that patients with a negative outlook had a utility value of 0.710, compared to 0.823 for those with a positive perspective. After one year of follow up, these values improved to 0.737 and 0.870, respectively, demonstrating that the utility gain of >0.1 for a positive view of life was maintained over time.[164, 167]

Optimism

Kung et al., 2006 examined the link between optimism/pessimism and HRQoL in 190 survivors of head, neck, and thyroid cancers in the United States. Using the Minnesota Multiphasic Personality Inventory to assess optimism/pessimism, and the SF-36 or SF-12 for HRQoL, the study reported that the most optimistic patients had a utility value of 0.560, while the most pessimistic had a utility value of 0.450.[165] Houten et al., 2021 mapped these results to EQ-5D utilities for thyroid cancer patients, revealing a 0.11 utility gain due to optimism.[167]

Individuals with APDS have an increased risk of malignancy from early in life;[9-11, 123] carcinomas (basal cell and papillary thyroid) have been reported in individuals with APDS in the literature.[10, 22, 168] Malignancy can have notable impacts on patient HRQoL and is discussed further in Question B.4 and Document B, Section B.1.4.2.

An improved outlook on the future and other positive impacts are often described by people with APDS who have received leniolisib:[169]

Patient living with APDS	*"Most of my childhood was spend in a hospital bed. I never really had a childhood...life has changed for the better, thanks to a newly discovered medical condition, dedicated doctors, and access to a drug trial with amazing results"*
Patient living with APDS	*"I feel like I took a life pill. I could breathe better and had more energy, and I could just do more things"*

Impact of absence of anxiety on HRQoL

Short et al., 2021 evaluated the EQ-5D-3L's effectiveness in screening for anxiety and depressive symptoms among 493 patients discharged from general internal medicine in Canada. In hospital settings, patients without anxiety and depressive symptoms had a utility value of 0.75, compared to 0.63 for those with anxiety. In community settings post-discharge, these values were 0.79 and 0.62, respectively, similarly indicating a utility gain of over 0.1 in the absence of anxiety, highlighting the importance of mental health on HRQoL.[166]

APDS has a negative psychological impact on individuals with the condition.[46, 74] A study from the Netherlands found that people with immune system disorders (IEIs) like APDS have significantly higher levels of mental health issues—distress, depression, anxiety, and somatisation—compared to age-matched controls, largely due to fear of infections, social isolation, maladaptation, and concerns about the future.[170, 171] This evidence aligns with findings from qualitative interviews with people with APDS, who reported feeling sad, isolated, socially isolated and frustrated as a result of living with APDS. 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,[46, 74, 172] an absence of anxiety in APDS would be expected to lead to a utility gain.

Table 20. Summary of published studies supporting the inclusion of the 0.1 utility gain

Description	Value	Source	Remarks
Impact of positive view	<u>At diagnosis</u> Positive view of life: 0.823 Negative view of life: 0.719 Utility gain due to positive view of life: 0.823–0.71=0.113 <u>At one year follow-up</u> Positive view of life: 0.870 Negative view of life: 0.737 Utility gain due to positive view of life: 0.87–0.737 = 0.133	Hedman et al., 2018[164]	SF-36 mapped to EQ-5D (as reported in Houten et al., 2021)[167]
Impact of optimism	Most optimistic: 0.560 Most pessimistic: 0.450 Utility gain due to optimism: 0.56–0.45 = 0.11	Kung et al., 2006[165]	SF-36 mapped to EQ-5D (as reported in Houten et al., 2021)[167]

Description	Value	Source	Remarks
Absence of anxiety	In hospital settings No anxiety nor any depressive symptoms: 0.75 Anxiety present, no depression: 0.63 Utility gain due to absence of anxiety: 0.75–0.63 = 0.12	Short et al., 2021[166]	EQ-5D-3L
	In community settings No anxiety nor any depressive symptoms: 0.79 Anxiety present, no depression: 0.62 Utility gain due to absence of anxiety: 0.79-0.62 = 0.17		EQ-5D-3L

Source: Hedman et al., 2018,[164] Houten et al., 2021,[167] Kung et al., 2006,[165] Short et al., 2021.[166]

Conclusion

As discussed in Document B, Section B.3.8.2, participants treated with leniolisib in Study 2201 reported improvements in aspects of APDS that were not modelled, such as increased energy during the study periods, or improvements in manifestations not captured within the model.[2, 8, 32, 33] People receiving leniolisib are also expected to benefit from a reduced emotional burden of APDS due to the lower expected risk of developing lymphoma and mortality, and increased hope due to the availability of a new treatment. Moreover, the model does not include various manifestations that leniolisib treatment has been shown to benefit, thereby underestimating its potential benefit. Additionally, while quantifiable data on caregiver impact is lacking, anecdotal evidence highlights positive improvements in caregivers' lives, further supporting the broader benefits of leniolisib beyond what the model captures.

Based on the published studies in Table 20, a utility gain of 0.1 is expected to capture the overall improvement in the wellbeing of patients associated treated with leniolisib. As the utility gain was an assumption based on the differences in utilities reported in previous published studies, the base case model assumed no uncertainty.

Uncertainty

Given the lack of data on uncertainty, and following accepted practices in previous technology appraisals,[173] a 10% standard error has been applied to other model inputs to account for uncertainty (see Question B.12). When the same percentage is applied for this assumption, this would result in a plausible range of 0.08 to 0.12 for the utility gain.

When this range is applied, the results of the deterministic sensitivity analysis remain relatively unchanged, with the top ten parameters with the greatest influence on the ICER remaining the same. This indicates that the base case ICER is robust to uncertainty in this assumption. Additionally, when applying this range within the PSA, again there was limited impact on the results, as illustrated in the scatter plot and cost-effectiveness acceptability curve below (Figure 10 and Figure 11).

Figure 10. Scatterplot of probabilistic results

Figure 11. Cost-effectiveness acceptability curve

Cost and healthcare resource use

B9. The company mentioned that three studies were identified that specifically reported on costs and HCRU in APDS (Section B.3.5 and Appendix I). However, the

company stated that none of these studies were deemed to provide useful evidence relevant to the decision problem for this evaluation. The EAG has not been able to locate the full text for two of these studies (Harrington 2023a and Harrington 2023b). Please could the company provide these papers?

Harrington 2023a and Harrington 2023b were both posters presented at the 2023 annual meeting hosted by the American College of Allergy, Asthma and Immunology and can be found online.

1. Katharina Büsch, HM, Heather M. McLaughlin, Amanda Harrington. Mortality in Patients With Activated Phosphoinositide 3 Kinase Delta Syndrome: A Systematic Literature Review. 2023. American College of Allergy, Asthma & Immunology (ACAAI) 2023 Annual Scientific Meeting (https://epostersonline.com/acaai2023/poster/p165), and
2. 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 (https://epostersonline.com/acaai2023/poster/p166).

B10. The company stated (Section B.3.5) that in the absence of published sources of evidence, cost/resource inputs included in the model were based on results from the quantitative survey of the Expert Consultancy project (Exercise 4). The EAG could not locate the reference provided (Pharming Data on File. Leniolisib Expert Perspective and Insight Consultancy to Inform UK Health Technology Assessment. 2023) in the company submission. Please could the company provide details of the Expert Consultancy project (Exercise 4)?

The company has shared the reference with the EAG alongside submitting this response.

B11. The company described the QoL impacts of APDS (B.1.4.2) including the limitations the condition has on the patients' ability to continue with work, education and daily living activities. The company stated that the analysis adopted a National Health Service (NHS) and Personal Social Services perspective (Section B.3), however no social care costs (i.e, home support, community services, health visitors etc) appear to be included in the model. Could the company clarify whether they consider APDS is associated with social care costs, and whether leniolisib is likely to affect these costs?

The company would like to clarify that the cost-effectiveness analysis presented in the CS adopted a NHS perspective (and not a Personal Social Services perspective).

Uncertainty

B12. When data were not available, the company assumed a 10% standard error around the model inputs to represent uncertainty (Section B.3.10.1). Could the company provide the rationale behind the assumption of a 10% SE?

When data sources do not provide enough information to estimate the variability around input parameters, it becomes necessary to make assumptions about the likely variability. A review was conducted by Lanitis, Muszbek and Tichy, 2014 on the methods used in all completed, full NICE single technology assessments published in 2013–2014. Due to the lack of available data, 68% of the reviewed TAs included at least one parameter where variation (standard error) was assumed and not informed by data.[173] In these cases, the standard error was assumed to be 10–30% of the mean.

The consistency of the probabilistic results (with a 10% standard error applied) with the deterministic results indicates the absence of non-linearities in the economic model. However, to to test the robustness of the probabilistic results to uncertainty in the model, a probabilistic scenario analysis has been run in which a 20% standard error around the model inputs has been assumed (when uncertainty was not available, taking the midpoint of the 10–30% range specifed above). Table 21 presents probabilistic results with the 10% (base case) and 20% (scenario) standard error assumptions, demonstrating that the choice of assumption does not substantially change results or alter the conclusions of the analysis. Figure 12 additionally presents the cost-effectiveness plane, cost-effectiveness acceptability curve and stability plot for the probabilistic scenario run assuming a 20% standard error around model inputs; net monetary benefit (NMB) stability is still reached before 1,000 iterations.

Table 21: Probabilistic results with 10% and 20% standard error assumptions

Assumed SE around model inputs	Probabilistic ICER (with 1.48x QALY weight applied)	Probabilistic ICER (unweighted)	Probability of cost-effectiveness at a willingness-to-pay threshold of £100,000/QALY
10% (base case assumption, as presented in the CS)	£[redacted]/QALY	£[redacted]/QALY	[redacted]%
20% (scenario)	£[redacted]/QALY	£[redacted]/QALY	[redacted]%

Abbreviations: ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, SE: standard error.

Figure 12: Probabilistic scenario results with a 20% standard error assumption

Abbreviations: NMB: net monetary benefit, QALY: quality-adjusted life year.

The OWSA was also re-run with the 20% standard error assumption (Figure 13). Compared to the OWSA presented in the CS (with a 10% standard error assumption), the age-specific rate of lymphoproliferation and resolution rate for lymphorroliferation are not in the top ten parameters with the greatest influence on the ICER in the updated OWSA; these are replaced with the advanced lung disease utility multiplier and gastrointestial disorders utility multiplier .

Figure 13: OWSA with 20% standard error assumption

Abbreviations: HR: hazard ratio, ICER: incremental cost-effectiveness ratio, IGRT: immunoglobulin replacement therapy (IRT), OWSA: one-way sensitivity analysis, SoC: standard of care (current clinical management).

Overall, the magnitude of the assumed uncertainty is of less consequence for this cost-effectiveness analysis.

B13. The EAG understands that hazard ratios for the impact of leniolisib on manifestations were estimated in the modified SEE of the Expert Consultancy

(Exercise 1). Could the company present the range of plausible HRs based on this exercise?

The company would first like to note that within the base case analysis, HRs for the impact of leniolisib on the incidence, severity and resolution of manifestations were based on a variety of evidence sources, including: the leniolisib clinical trial programme (Study 2201 Part II and 2201E1),[2, 8, 32] the leniolisib EAP,[57] and the modified SEE (Exercise 1 of the Expert Consultancy).[6] As outlined in Table 41, Document B, Section B.3.3.4 of the company submission, evidence from the leniolisib clinical trials was given the highest priority, followed by the EAP data, with the modified SEE data used to address any subsequent gaps.

In Exercise 1, the modified SEE, UK clinicians were provided with relevant natural history data from ESID and findings from Study 2201 Part II, Study 2201E1, as well as real-world evidence. Subsequently, clinicians were then asked to provide their estimates for the upper and lower plausible limits of manifestation occurrence under leniolisib treatment. To mitigate uncertainty, the midpoints of their estimates were used in the primary analysis for manifestation occurrence and clinicians had the option to indicate if they felt particularly uncertain about answering a question (see the third scenario analysis below).[6]

During the clarification call on the 20th June 2024, the company agreed to re-share the Expert Consultancy report which includes the plausible HRs for the impact of leniolisib on manifestations based on the midpoints of the clinicians' upper and lower estimates (**primary analysis**). Please refer to the embedded Microsoft Excel spreadsheet in Appendix 9.1.4 of the report for these values, sheet: *Ex 1 Results Base Case.*[6]

To explore the uncertainty in the HRs calculated as part of the Expert Consultancy analyses, sensitivity analyses and three scenario analyses were conducted. The findings for these analyses can be found within the embedded Excel (Appendix 9.1.4) in the Expert Consultancy report, as detailed below:[6]

1. In the **first scenario analysis**, the mean upper limit for SoC and the mean lower limit for leniolisib were used. In cases where the lower limit of leniolisib was 0, the resulting HR value was 0; the results can be found in sheet: *Ex. 1 Results Scen Analysis 1* of the Excel file. HR values of 0 suggest that leniolisib reduces the incidence of people with APDS experiencing the manifestation to 0%.
2. In the **second scenario analysis**, the mean lower limit of SoC and the mean upper limit of leniolisib were used. In cases where the mean lower limit of SoC was 0, the resulting HR value was 0; the results can be found in sheet: *Ex. 1 Results Scen Analysis 2* of the Excel file.
3. The **third scenario analysis** involved using the results of sensitivity analyses for Part 1 and Part 2 in which responses (for manifestation rates) marked by clinicians as being particularly uncertain were removed. For this scenario analysis, the midpoint estimates from Part 1 and Part 2 were used (per the primary analysis). Exclusion of the uncertain values resulted in minimal changes compared to the primary analysis, indicating that clinicians were confident in their responses, and that the primary analysis HRs were plausible. The results can be found in sheet: *Ex. 1 Results Scen Analysis 3* of the Excel file.

The HRs from the first and second scenario analyses differed from the primary analysis, which is a reasonable outcome as the scenario analyses utilised combinations of the upper and lower limits for SoC and leniolisib, producing HRs lying at the extreme bounds of clinical plausibility,

whereas the primary analysis used the midpoint estimates to mitigate uncertainty in the clinicians' responses (following guidance in Bojke et al., 2021).[149] The third scenario analysis (removing uncertain responses) resulted in minimal changes to the primary analysis, with the HRs being comparable, indicating that clinicians were confident in their responses. Therefore, use of the midpoint estimates in the primary analysis provides the most plausible HRs for the impact of leniolisib on manifestations of APDS.

B14. The company conducted a scenario analysis (Scenario 1, Section B.3.10.3) in which the impact of leniolisib on survival was calculated through manifestation-specific mortality risks. The company stated that a model calibration was conducted to ensure visual fit of the predicted survival curve to the APDS Kaplan–Meier curve in standard care. Given that this calibration value has a relatively large impact on the cost-effectiveness results:

a) Could the company provide more information on how this calibration value was determined?

Due to absence of data, mortality HRs associated with manifestations were obtained from a CVID (common variable immunodeficiency) study (Odnoletkova et al., 2018).[174] The estimates from the CVID study provide information on the mortality HR of CVID patients with the specific manifestation compared to CVID patients without the specific manifestation. Therefore, it is informative of the relative impact of manifestations on mortality compared to each other. However, the underlying distribution of these manifestations in APDS is known to be different, therefore APDS patients without the specific manifestation are likely to suffer from a different collection of manifestations compared to CVID patients, and therefore the absolute value of the HRs is unlikely to represent the true impact of the specific manifestation in APDS. To address this issue, a calibration factor was implemented in the model to ensure that predicted overall mortality for the standard of care arm is in line with observed overall mortality in APDS patients. The calibration factor was a simple static multiplier of the hazard of mortality. The value was determined by assessing the visual fit of the calibrated prediction using the manifestation-specific HRs for a cohort starting from birth based on visual fit to the APDS-specific KM curve (Hanson et al., 2024).[23] The use of calibration was also supported by HTA experts.[5]

b) Has the company conducted sensitivity analysis regarding the calibration value used in this scenario analysis?

The sensitivity analyses were carried out around the base case, which did not include the manifestation-based mortality prediction. However, the structural assumption of using the manifestation-based mortality prediction (instead of the APDS-specific mortality) was tested in the scenario analyses.

c) Could the company provide a plausible range of calibration values?

The figures below show the impact of different assumptions around the calibration factor (ranging from no calibration, to a calibration factor of [redacted]). These graphs indicate that the plausible range of the calibration factor should be [redacted]. The model uses a factor of [redacted] based on visual

inspection, because higher values underestimate long-term survival for the standard of care arm, while lower values of the calibration factor overestimate survival.

Figure 14. APDS-specific survival with [redacted] calibration factor applied

Figure 15. APDS-specific survival with [redacted] calibration factor applied

Figure 16. APDS-specific survival with [redacted] calibration factor applied

Figure 17. APDS-specific survival with [redacted] calibration factor applied

Figure 18. APDS-specific survival with [redacted] calibration factor applied

Figure 19. APDS-specific survival with [redacted] calibration factor applied

Results

B15. Priority question: The company's base-case cost-effectiveness results presented in Section B. 3.9.1, included a 1.5 QALY weight which has a large impact on the ICER. The EAG notes NICE guidance states that for highly specialised technologies, the severity of the condition has already been implicitly captured in the selection of technologies for evaluations. Therefore, no additional QALY weighting for the severity of disease is applied.{NICE, 2022 #3}

Could the company please ensure that the cost-effectiveness base-case analysis is conducted without this QALY weight based on the relevant statement in the NICE guidance?

When developing the base-case analysis, the company referred to section 6.2 of the NICE methods and processes guide (PMG36), specifically the section on '**Decision modifiers: size of benefit for highly specialised technologies**'.[162] This section of the guidance states that:

> *6.2.23 For highly specialised technologies, the committee will consider the size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of the technology to fall within the highly specialised technologies £100,000 cost per QALY level.*
>
> *6.2.24 For this weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained.*
>
> *6.2.25 Weighting is applied as described in table 6.2 below:*

Table 6.2: QALY weightings for size of benefit for highly specialised technologies

Incremental QALYs gained (per patient using lifetime horizon)	Weight
Less than or equal to 10	1
11 to 29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

The current NICE processes and methods manual does not comment on whether undiscounted or discounted QALYs should be used to calculate the QALY weight. Therefore, looking to precedence:

- In their final guidance for a number of previous evaluations, NICE have published and used undiscounted incremental QALYs to calculate QALY weights (including, but not limited to, HST7, HST16, HST27, HST28 and HST30);

- Previous NICE guidance from 2017 (now unavailable) stated to use undiscounted QALYs to calculate the QALY weight.

Therefore, the company used undiscounted incremental QALYs to calculate the QALY weight, taking the full magnitude of the QALY benefit with leniolisib into consideration. Unweighted and undiscounted QALY gains under the company's deterministic base-case analysis were 14.8. Considering then the guidance outlined in Table 6.2, this would correspond to a weighting of 1.48.

The above guidance implies that QALY weighting should be applied to the (assumedly discounted) incremental QALYs, to allow the cost effectiveness of the technology to be compared against a constant threshold of £100,000 per QALY gained. The CS aligned to this guidance, applying the weighting to the discounted incremental QALYs (and hence to the ICER) for leniolisib. However, to clarify, Table 60 in the CS presented the **unweighted and weighted** determinstic incremental QALYs and ICER for leniolisib, in acknowledgement that the EAG and Committee may wish to consider both weighted and unweighted economic results.

Table 60 from the CS has been reproduced as Table 22 below, with the unweighted economic results now labelled more clearly:

- Unweighted incremental QALYs and ICER have been presented, with the 1.48x weighting instead applied to the cost effectiveness threshold, yielding a threshold of £148,000/QALY gained;
- Weighted incremental QALYs and ICER have also been presented, to allow comparison to the cost effectivness threshold of £100,000/QALY;
- The interpretations of both presentations of results are the same.

As demonstrated in Figure 25 of the CS (scatterplot of probabilistic results), the majority of the iterations in the probabilstic analysis produced discounted, unweighted QALY gains for leniolisib larger than the deterministic base case QALY gain of 10.46. Additionally, the scenario analyses presented in the CS were generally associated with discounted, unweighted QALY gains for leniolisib near to the determinstic base case. Together, these results indicate that there is relative certainty in the QALY benefits estimated by the economic model, further justifying the weighting presented in the CS.

Table 22: Deterministic base-case results (with proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Unweighted results Cost effectiveness threshold to compare ICER against: £148,000/QALY		Weighted results Cost effectiveness threshold to compare ICER against: £100,000/QALY	
						Incremental QALYs	ICER (£/QALY)	Incremental QALYs	ICER (£/QALY)
Leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.46	[redacted]	15.46	[redacted]
Current clinical management	1,587,334	34.81	[redacted]	-	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Section C: Textual clarification and additional points

Reference confirmation

C1. Please can you confirm if reference 87 cited in appendix N2.2. of Document B *(Pharming Data on File. Comparative efficacy of leniolisib (CDZ173) versus standard of care on rates of respiratory tract infection and serum immunoglobulin M (IgM) levels among individuals with activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS): An externally-controlled study. Submitted Manuscript. 2024*.) is filed as *Pharming_Infections and IgM Combined Manuscript_Submitted_ 28Feb2024.*

Yes, this is correct.

C2. Can you confirm if reference 64 cited in Document B (64. 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.) corresponds to the document filed as *Pharming_Global Physician EAP Survey_13Dec2023*

Yes, this is correct.

C3. The company references a modified Delphi panel to determine meaningful outcome domains and clinically meaningful differences for the surrogate endpoints (Document B, section B.2.4.2, page 68). Can you confirm reference 266 cited in document B corresponds to the document filed as *Pharming_Delphi Report_Meaningful_Change_v4_1Mar2024*

Yes, this is correct.

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Appendix

Supplementary Detail for Clarification Question A.14

Table 23. Details of individuals with APDS who developed lymphoma after treatment with leniolisib

Case ID Sex/Age Country Source	Event PT Time to onset Outcome	Drug start date Action taken Stop date Causality	Narrative
PHAFI2022000816 F/24 Finland EAP	Hodgkin's disease 2y 11mo Fatal	13APR2020 Withdrawn 24MAR2023 Not related/Not related	Patient started leniolisib on 13 Apr 2020, which resulted in diminishing of her massive lymphadenopathy, improvement of immunological parameters and marked improvement of general health. In May 2022, enlarged epigastric lymph nodes were observed but needle biopsy did not reveal a specific diagnosis. In Nov 2022, patient became EBV positive, and later developed persistent EBV viremia as well as EBV positive intestinal and lymph node biopsies. Patient also developed weight loss, anemia, fatigue and infections. An open lymph node biopsy on 30 Mar 2023 revealed classic Hodgkin's disease. Leniolisib was discontinued and patient was referred to the oncology

			department for treatment. However, disease progressed and patient died on 12 Jul 2023.
PHAUS2022000369 F/20 US Sponsored study	Hodgkin's disease 2y 20d Not recovered	04JUN2020 Withdrawn 20JUN2022 Not related/Not related	Patient included in study CCDZ173X2201E1 (Study 2201E1). Patient presented to the ER on 01 Jun 2022 with COVID-19 infection and pancytopenia. Patient required 10 units of packed RBCs for correction of severe anemia. Lymph node biopsy was performed due persisting fever, cytopenias and EBV viremia and resulted in the diagnosis of Hodgkin's lymphoma. Leniolisib was withdrawn and chemotherapy was started. At the last contact date patient was still receiving chemotherapy.
PHAUS2024000053 M/24 US Spontaneous Specialty Pharmacy	Lymphoma About 2 mo Not reported	10NOV2023 Continued NA Not reported/Not related	Patient reported in Jan 2024 having been diagnosed with lymphoma and starting chemotherapy soon. He was on leniolisib since 10 Nov 2023 and treatment was continuing. No further information is available.

Footnotes: Pharming Data on File.[5]

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]

Clarification questions – Addendum: Additional Evidence

July 2024

Clarification questions A4 and B8

In response to the External Assessment Group's (EAG) clarification questions A4 and B8, the company would like to submit additional evidence from an Australian case report. The following statement was shared by a physician from an individual with APDS after receiving leniolisib treatment for approximately 9 months:

Patient receiving leniolisib for ~9 months	*"Since commencement of the leniolisib I have noticed a change in health that has drastically improved my life in a number of ways. My lung saturation has increased from my base line of 87-92 to often above which has not occurred in years, I seem to have had a drastic allergy reduction from consuming gluten to the point I hardly have a reaction if I'm naughty and consume and the most fascinating is the reduction in health fluctuations as an immune compromised person and considering my primary antibiotic has been having supply issues since September 2022, is honestly mind blowing. These are just three of the fantastic benefits I have noticed whilst on the medication, there are many more as well but I wish to say that whatever the outcome your expecting, expect the unexpected, this medication is fabulously life changing for anyone with an immune deficiency.* *I do honestly think that this medicine has improved my life quite significantly especially when comparing to Sirolimus. It's not a cure but it's damn sight close."*

This statement highlights the profound impact of leniolisib on improving clinical manifestations as well as quality of life after only a few months on treatment, making it a potentially transformative therapy for individuals with APDS. It also highlights the importance of reducing reliance on treatments which may face supply chain issues such as antibiotics.

Clarification question B3

In response to the EAG's clarification question B3, the company would like to submit additional evidence from an advisory board meeting held on 2nd July 2024 involving six UK clinicians, including immunology and bone marrow transplant experts specialised in inborn errors of immunity (IEI), all with experience in treating people with APDS.

The meeting included focused discussion on the implications of the mechanism (MoA) of leniolisib as presented in the Cant et al. paper elucidating the mechanisms of action of different PI3K inhibitors. During the meeting, the clinicians were posed with the question: "With the MoA [of leniolisib] in mind, do you think there are any reasons that the efficacy of this treatment might change over the long term?". In consensus, the physicians agreed that based on leniolisib's mechanism of action, they did not foresee any likelihood of treatment response diminishing over time. One clinician also clarified that treatment effect waning in this context would be restricted to biologics (e.g. monoclonal antibodies).

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Immunodeficiency UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Immunodeficiency UK is a small, registered charity. We support people and families affected by primary and secondary immunodeficiency work through a range of activities including providing a helpline, medically reviewed information, patient events and hardship grants. Our mission is to work with patients, healthcare professionals and other relevant organisations to ensure those affected have the knowledge needed to manage their condition effectively and to ensure their health needs are understood and addressed by those involved in policy and delivery of healthcare. We currently have 1400 members. We are funded through community fundraising, trusts and foundations and pharmaceutical companies. The latter currently include Takeda, CSL Behring, LFB Ltd and Grifols. We have a published policy of how we work with pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.]	None in the financial year 2023-2024. Immunodeficiency UK received funding in 2022 (£10,000) from Pharming for the development of five patient stories about the importance of an early diagnosis of PID (a mixture of PID conditions) for Rare Disease Day, addition of information on APDS (developed with our medical panel) and two patient stories about APDS, which are available on our website. This information carries the following statement 'This patient story was developed with the help of funding from Pharming to Immunodeficiency UK in 2022. Pharming had no contact with the author and no editorial control.' Over the last 12 months we have developed two other patient stories about APDS.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No. It is our policy not to accept funding from these sources.

5. How did you gather information about the experiences of patients and carers to include in your submission?	Through telephone conversations with affected individuals and their carers, developing patient stories and through a joint survey project with NICE. The survey involved the co-production of survey questions, NICE hosting the survey and ID UK highlighting the survey to people affected by APDS through our e-newsletter, social media and reach out to immunology specialist centres. There was a formal survey collaboration agreement between ID UK and NICE. A report of the findings is found in Appendix 1. The survey attracted 14 responses: four people were directly affected by APDS and ten identified themselves as a carer, a family member or friend of the family. These included parents/family members of affected children under the age of 12 years. APDS is a life-long condition and based on mortality data, children affected by APDS are likely to reach 12 years of age and over so would be offered this treatment. Therefore, their opinion is valid and it is important that their views are taken into consideration.
6. Living with the condition. **Impact on daily life and carers.**	The impact on APDS on daily life is significant. Respondents reported affects on family life (n=8), daily activities (n=7), ability to do hobbies (n=6), ability to socialise (n=5), ability to work (n=4). Of 13 respondents only four reported satisfaction with quality of life. 10 respondents reported an extreme or moderate amount of tiredness associated with having APDS. A major factor was the impact on the ability to attend school/educational activities (n=10), with 12 respondents reported significant days off. The range was several weeks each term, 1-4 years. *Recurrent infections, stunted growth, hearing issues impacting learning in school, ability to do physical sport, coordination issues.' Mum to an affected child.* *'Ear and lymph glands problems. Behind in schoolwork and development both socially and academically'. Mum to an affected child.* Ten respondents reported that APDS **impacted their mental health.** Reasons were burden of care, isolation and loneliness, depression, frustration. A major concern is worry of the risk of infection with 11/13 respondents reporting an extreme amount of concern. The vulnerability to COVID was mentioned specifically. Eleven respondents reported an extreme or moderate extent of worry about future health. *"Makes me feel so down and depressed, isolated". "Anxiety, uncertainty, having a condition no one understands."*

	Pain and discomfort: Only 3 of 12 respondents reported little or no pain associated with having APDS. Four respondents reported extreme/moderate pain (scale 7-10, where 10 is extreme pain). '*Xxxx struggles with discomfort in her ears, stomach and chest. She has had reoccurring lung collapse which would be more on a level of 10 for pain when this occurs.' Mum to an affected child.* *'I'm struggling. I suffer from swollen lymph nodes, lymphoid polyps, enlarged spleen. I'm continuously out of breath'. Patient directly affected by APDS.* *'Tough, exhausting, damaging, poorly, sick, irritable from coughing and all the infections, painful'. Adult patient directly affected by APDS.* Four respondents reported an impact of APDS on **carer's ability to work** with subsequent loss of income. *'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.' Mum to an affected child.* *'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.'* *"delayed development so not potty trained and can't wash himself".* *"2-3 physio sessions a day, medicine administrations, weekly subq infusions, frequent soiling as on antibiotics regularly".* **On living with APDS**: *'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, etc'* Tough, exhausting, damaging, poorly, sick, irritable from coughing and all the infections, painful.'

	"Tiredness and chest infections are a major concern as well as the mental anxiety the condition causes." **Symptoms which were reported as having an extreme impact** were bronchiectasis, respiratory infections, chronic cough, infections, autoimmunity problems, enlarged lymph nodes, gastrointestinal problems, enlarged spleen and hearing problems. **Impact of disease burden on patients and the NHS.** Average number of outpatient visits over the last twelve months was 24.6 visits (n=13; range 2-200 visits). Average number of days in hospital over the last twelve months was 17.6 days (n=13; range 0 -80 days). These results highlight the impact on individuals and families in spent of time spent managing the condition and disruption to their lives through time spent in hospital (Table 3; Appendix 1).

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	A wide range of treatments are used in APDS. This was reflected in the survey data (table 2, Appendix 1). The burden of treatment is high but was variable within the respondents (Appendix 1), reflecting the differences in how having the condition APDS can impact on patients. Three respondents were taking 5 treatments, one patient had four treatments, one had 3 treatments, four had 2 treatments and five had 1 treatment (immunoglobulin only). All survey respondents reported they or the patient were currently on medication: 12 were on immunoglobulin therapy, 9 prophylactic antibodies, 5 prophylactic anti-virals, 6 immunosuppressants and 3 were taking Sirolimus. Respondents reported symptoms that are not addressed by current treatments (Page 13, Appendix 1).

8. Is there an unmet need for patients with this condition?	APDS is an ultra-rare disease with no approved therapies and is considered by the clinical community as a serious life-threatening condition. It is our understanding that there are 41 people in the UK with APDS. There is an unmet need for treating the consequences of having a dysregulated immune system which Leniolisib can address. Leniolisib is a targeted therapy and represents a 'first of its kind' treatment to address the fundamental cause of immune dysfunction in people with APDS by acting specifically on the overactive PI3K delta kinase. The drug Leniolisib can help address autoimmunity and malignancy (lymphoma) which occur in APDS. Current therapeutic options such as antibiotics, immunoglobulin therapy only manage the symptoms of this immunodeficiency and help with infections. Having access to Leniolisib could result in reduced hospital admissions, lower use of antibiotics, and health improvements may translate into ability to have a full education and working life and improved quality of life. All (5 of 5) survey responses thought that everyone should have access to Leniolisib and all (8 of 8) survey respondents would recommend Leniolisib to other patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Six of 14 respondents had been treated with Leniolisib (one, only for one month), with one respondent saying they were unsure if they taking this medication. Five survey respondents reported benefits: • Reduction in use of antibiotics (n=2) • Bringing bloods (blood counts) up (n=1) • Increasing energy and appetite (n=1) • Reducing hospital admissions (n=1) • Reducing lymph nodes (n=1). • Reduced coughing (n=1). *'xxx had been on antibiotics for 5 years with several hospital additions where so as starting treatment to date of 8 months xxx has only had 3 antibiotics and no hospitial additions'. Mum to an affected child.* '*Reduced coughing, reduced the amount of need of antibiotics.' Person directly affected who is taking Lenio.* *'Reduced lymph nodes. More appetite and energy.' Person directly affected by APDS.* *'100% would recommend the medication. As a parent you want what is best for your children, 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 then what she is today and for that reason I would always recommend it.' Mum to an affected child (<12 years old) and who is on Leniolisib.* HSCT is the only curative option for APDS. Leniolisib could act as a bridging treatment to HSCT by stabilising the immune system and preventing organ damage that can decrease the chances of a successful outcome (see section 12).

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Three of six survey respondents who were taking Leniolisib reported drawbacks. This included the possible side effects listed (N=1), having mouth and tongue ulcers for the first time (N=1), and Leniolisib not tackling the infection damage that was caused before starting the Leniosilib (N=1), highlighting the need for improved diagnosis (the majority of respondents reported a time to diagnosis of greater than three years).

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The survey results (Appendix 1) indicate that the effects of having APDS can vary between individuals. This is not a surprise as clinicians tell us that some patients are more severely affected than others. It is widely known that the same genetic abnormality can cause different effects in different people. This variability may arise from complicated interactions between genes, and other factors related to the patient and his or her environment. The fact that gene defects can have such variable effects has been known for many years. This variation of severity between individuals is also reflected in the survey findings on treatments taken to manage symptoms and outpatient and in hospital stays. Clinicians would be able to select the patients who would benefit most and develop guidelines for the treatment of APDS to ensure all those affected get the best standard of care.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are no specific ethnic groups that are affected by APDS however people with an ethnic background may find it difficult to find a suitably matched unrelated donor for HSCT. Information from the charity DKMS, who, with the help of other partners, help recruit stem cell donors, states that *'Patients from black, Asian or other minority backgrounds have a 20% chance of finding the best possible blood stem cell match from an unrelated donor, compared to 69% for northern European backgrounds.'* The availability of Leniolisib for those patients who are unable to have HSCT will help tackle this inequality. *'XXX 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.'* Mum to a child affected by APDS.

Other issues

13. Are there any other issues that you would like the committee to consider?	Leniosilib could be a bridging treatment to the potential of a cure by HSCT by normalising the immune system in APDS.

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Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with APDS can have a profound impact on physical, mental health, daily and family life and quality of life of those affected, their carers,and families. • Patients and carers reported significant health benefits of taking Leniolisib including reducing lymph nodes, reducing hospital admission, improved energy levels and reduction in antibiotic use. • Leniolisib may reduce inequality by improving health of people who are unable to benefit from HSCT because of the lack of tissue-matched stem cell donors. • There is overwhelming patient support for the availability of Leniolisib for the treatment of APDS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - **YES** or NO

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Impact of APDS survey on patients and their carers

Activated PI3K delta syndrome (APDS) is a rare primary immunodeficiency. About 40 people in the UK are known to be affected by the condition.

In April 2024 Immunodeficiency UK worked with NICE to develop an online survey to help understand the impact of the rare condition APDS on those affected and their carers. The evidence was used for NICE's technology appraisal of the drug Leniolisib for the treatment of APDS.

The survey was publicised in Immunodeficiency UK's newsletter, on social media and reach out to immunology centres.

Fourteen people with experience of APDS responded to the survey.

Key findings from the survey

- Most respondents reported a time to diagnosis of greater than 3-5 years.
- APDS was shown to have a significant impact on daily and family life affecting education, ability to work, socialise, carrying out daily activities, family activities and hobbies. Significant impacts were also described on carers and siblings of those affected. Only 30% of respondents reported satisfaction with their quality of life.
- Physical pain and discomfort and extreme tiredness were associated with having the condition.
- APDS impacts on mental health with concerns about the health of the person affected, with extreme anxiety about getting infections. Factors impacting on mental health included the burden of treatment and care, dealing with pain, coping with feelings of isolation and loneliness and uncertainty about the future.
- Symptoms of APDS which had the most impact on those affected were bronchiectasis, respiratory infections, chronic cough, autoimmunity problems, hearing problems, enlarged lymph nodes, gastrointestinal problems and having an enlarged spleen.
- Respondents reported an average of 24.6 outpatient visits (range 2 - 200) and 17.6 days in hospital (range 0 – 80 days) over the last year.
- The treatment combinations used to manage APDS varied between individuals. Four respondents indicated they were taking four to six medications. The most used therapies were immunoglobulin therapy, prophylactic antibiotics, followed by immunosuppressants, prophylactic antivirals and Sirolimus.
- There remains an unmet need for treatment of symptoms not addressed by current treatments.
- Six respondents had been treated with Lenioslib. Of these five reported health benefits. These included a reduction in lymph node size, improved blood counts, increased energy and appetite, reduced use of antibiotics and hospital admissions.
- Respondents gave overwhelming support for the drug Leniolisib to be made available to people with APDS.

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- **About the survey respondents**

Fourteen people with experience of APDS responded to the survey.

Four respondents were directly affected by APDS. Ten identified themselves as carers, a family member or friend of the family of a patient with APDS.

Six people confirmed they were being treated with Leniolisib.

Self-reporting of respondent's ethnic group were:

10 respondents: English, Welsh, Scottish, Northern Irish, British

1 respondent - Any other white background

1 respondent - Asian

1 respondent - White & Asian

1 respondent – Chinese.

Type of responder	Number of respondents	Sex, age of respondents
Directly affected by APDS	4	*1 male; aged 58. 3 females; ages 21, 37 and *47.
A carer of a patient with APDS	7	2 female; 5 male carers responded. Age range of child affected: 3 -12 years old.
A family member or friend of the family	3	2 female and 1 male responded. Age range of child affected: 3-14 years old.

* Family members also affected by APDS.

- **Time to diagnosis**

The majority of respondents reported a time to diagnosis of greater than 3 years (N=9).

Diagnosis:

"Doctors need to be educated on the condition".

"Undiagnosed for 5 years was so scary, several hospital additions with pneumonia, struggling to breathe, eat and sleep. Parents and medical professions should question if the child has been on several recurring antibiotics and admitted with recurrent chest infections."

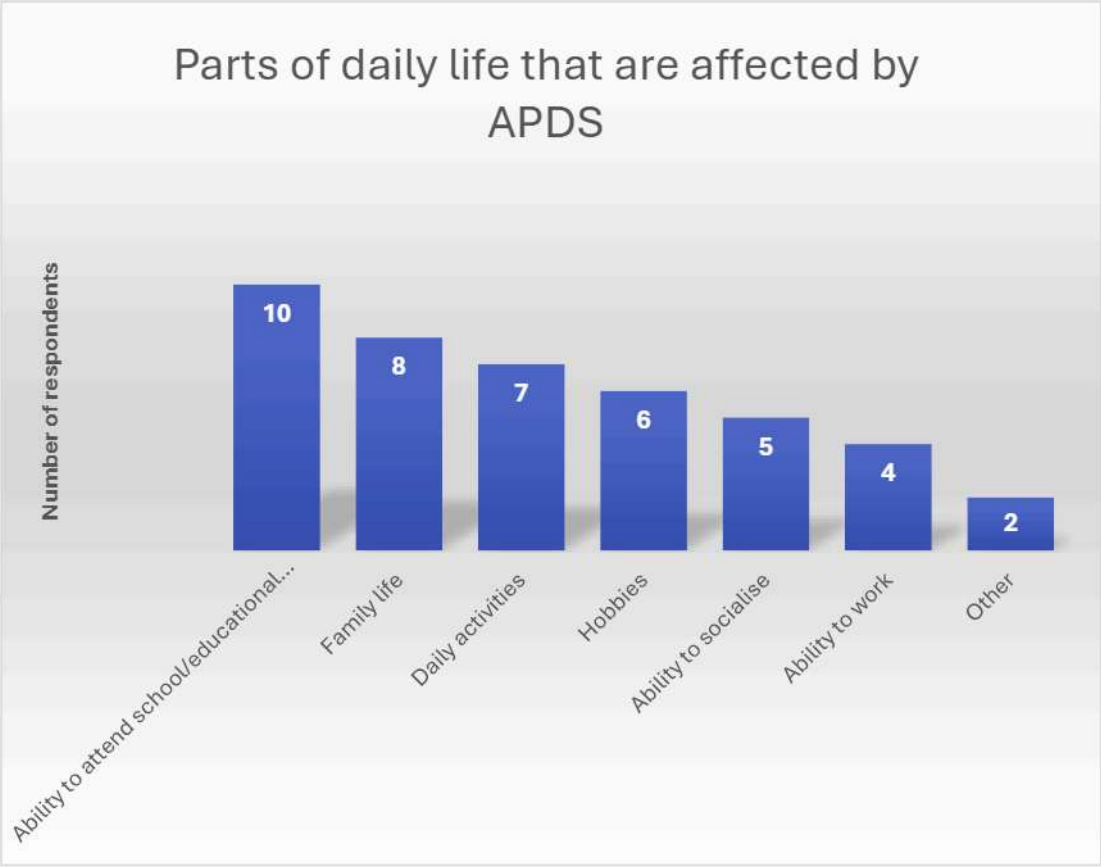
"more awareness needs to be made about this condition. All the doctors who have tried to help [patient] in the past didn't even know what this condition was when [they] was finally diagnosed. We struggled to get help for 7 years which has led to horrific lung damage. More awareness would help other families who may be suffering from the disease but are unaware they even have it. We as a family are trying our best to do our part in making this condition known."

"Infant screening at the heal prick test would have saved a lot of problems."

- **Impact on daily life**

The impact of APDS on daily life is significant.

This included the ability to attend school/educational activities (N=10). 12 respondents reported significant days off school/college. This included several weeks each term (N=1), 1 year (N=1), 2 years (N=1), 4 years (N=1), and unable to attend (N=1).



Impacts:

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

"tiredness and infections". "Emotionally distress"

"Torture".

"[Patient] fell poorly around 1 years old. Despite us not having a diagnosis we knew something was wrong as she was constantly poorly and getting infections. From this point up until the age of 7 [patient] struggled to mix with other children and has only been able to complete a full school year without hospital admission once. This affected her ability to maintain friendships with her peers and to keep up with her education."

"Lots of vomits and coughing. Took many sick days off school. Had lots of trips to the GP and hospital"

"Bronchiectasis from APDS - 2/3 daily physio and 3 monthly IV hospital antibiotics".

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

"Recurrent ear infections resulting in holes in ears so washing and swimming difficult."

"psychological and emotional effects"

- **Impact on education**

This included the ability to attend school/educational activities (N=10). 12 respondents reported significant days off school/college. This included several weeks each term (N=1), 1 year (N=1), 2 years (N=1), 4 years (N=1), and unable to attend (N=1).

Missing education

"Missed several days of school. Missed out on dance / gymnastics due to being ill. Walking, plays at the park."

"Several weeks of school each term."

"[Patient] missed almost the whole of reception, at least 3 months of year 1, 2 months of year 2 and thankfully only 3 weeks of year 3."

- **On ability to work and loss of income**

Four respondents also reported the impact APDS had their ability to work. One respondent was not able to work as they looked after their 4-year-old child with APDS.

Impact on work

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

"Not working as a results to looking after my son."

Loss of income – *"Very much so as one household working and not entitled to any help/benefits".*

- **Impact on mental health**

Ten respondents reported that APDS impacted their mental health. Reasons included burden of care (N= 3), frustration (N=3), moderate and extreme anxiety (N=2), isolation and loneliness (N=2), confusion (N=1) and depression (N=1).

Mental health impacts:

"Makes me feel so down and depressed, isolated". "Frustration." "Can be lonely."

"Not being able to most things my son should be doing has impact on his mental health."

"Tearful. Frustrated, Unsure if he actually has constant physical or mental pain."

"The amount of hospital appointments and receiving medical care each week at home".

"Recurrent blood tests and hospital appointments."

"Anxiety, uncertainty, having a condition no one understands, frustration at having to have weekly infusions."

"When [patient] cannot go and play with his friends or when [patient] had to miss a family trip away due to being hospitalised [they] asked "why me"."

- **Impact on mobility**

Five respondents reported an impact on mobility.

Impacts were:

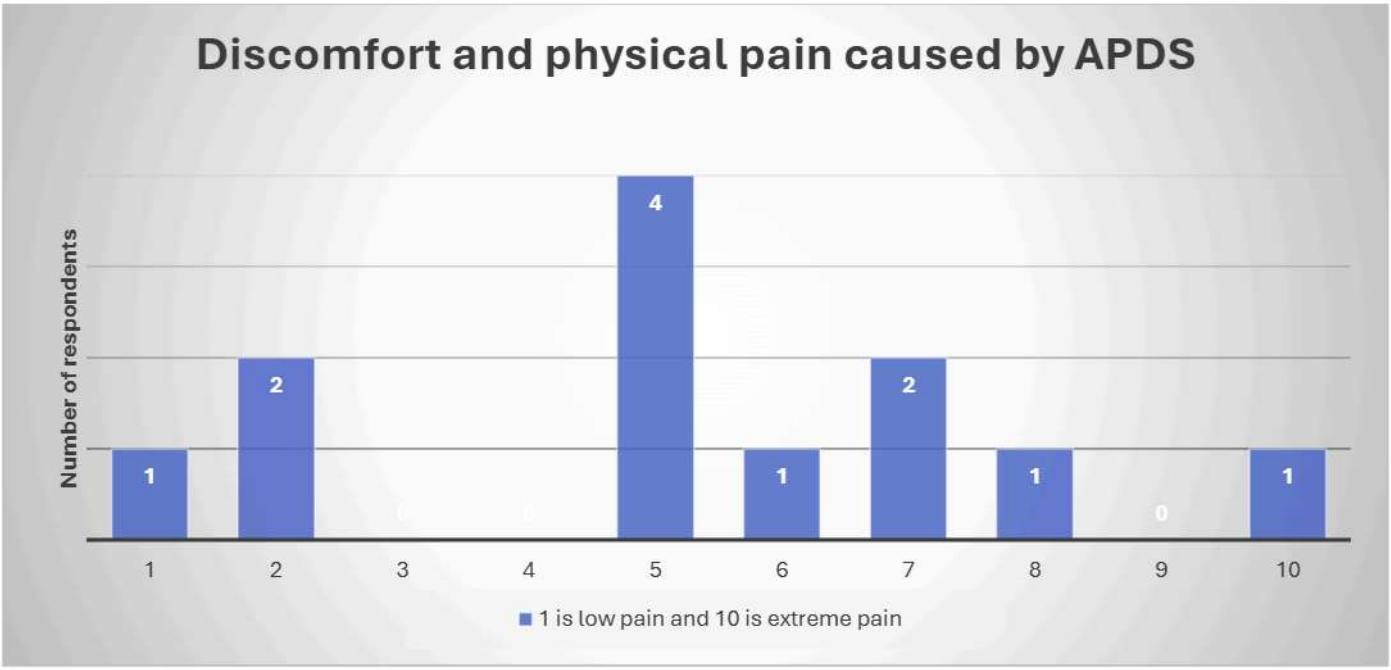
"Painful, breathless, exhausted." "Hypermobility in limbs". "Can get dizzy or lightheaded."

"Slow at learning to crawl and walk. Unable to walk for long distances".

"Legs after the immunoglobulin treatments but so cannot walk as far as his peers."

- **Physical and pain discomfort**

Twelve respondents reported their pain and discomfort in relation to having APDS. One respondent reported that pain had an extreme effect on doing what they needed to do. Six respondents reported a moderate effect and 5 a little. Only 1 respondent said it had no effect.



Examples of physical pain experienced:

"On my worse days I am in pain from weak joints, or headaches from sinus flare ups, chest always hurts with coughing so hard."

"[Patient] struggles with discomfort in [patient's] ears, stomach and chest. [Patient] has had reoccurring lung collapse which would be more on a level of 10 for pain when this occurs."

"pain in knees." "Hands can lock." "Discomfort." "Frequent infections." "Legs".

"[Patient] will wake up in the middle of the crying out in pain."

"Only when having blood tests and weekly subcutaneous infusions."

- **Impact on different aspects of quality of life**

Three respondents reported that they experienced an extreme amount of tiredness in relation to having APDS, with a further 7 respondents being moderately affected (Table 1).

Six of 13 respondents indicated they were extremely worried about their health, with a further 5 respondents moderately affected.

A major concern was worry of the risk of infection with 11 of 13 respondents reporting an extreme amount of concern.

Table 1

Quality of life factor	Rating: An extreme amount	A moderate amount	A little	Not at all	No of responses
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

Fears about infections

"Makes me worried when I get an infection the long term affect it is having on me."

"I'm terrified to go out or I'm always poorly with either a chest infection or my head feeling like it is about to explode."

"As a mum I worry a lot about [patient]. Covid being our biggest fear due to how damaged [their] lungs are from the condition. We managed to shield from Covid and [they] didn't catch the virus untill 2023. [They] had a collapsed lung from Covid so we are very careful about who {they] mixes with who are unwell."

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

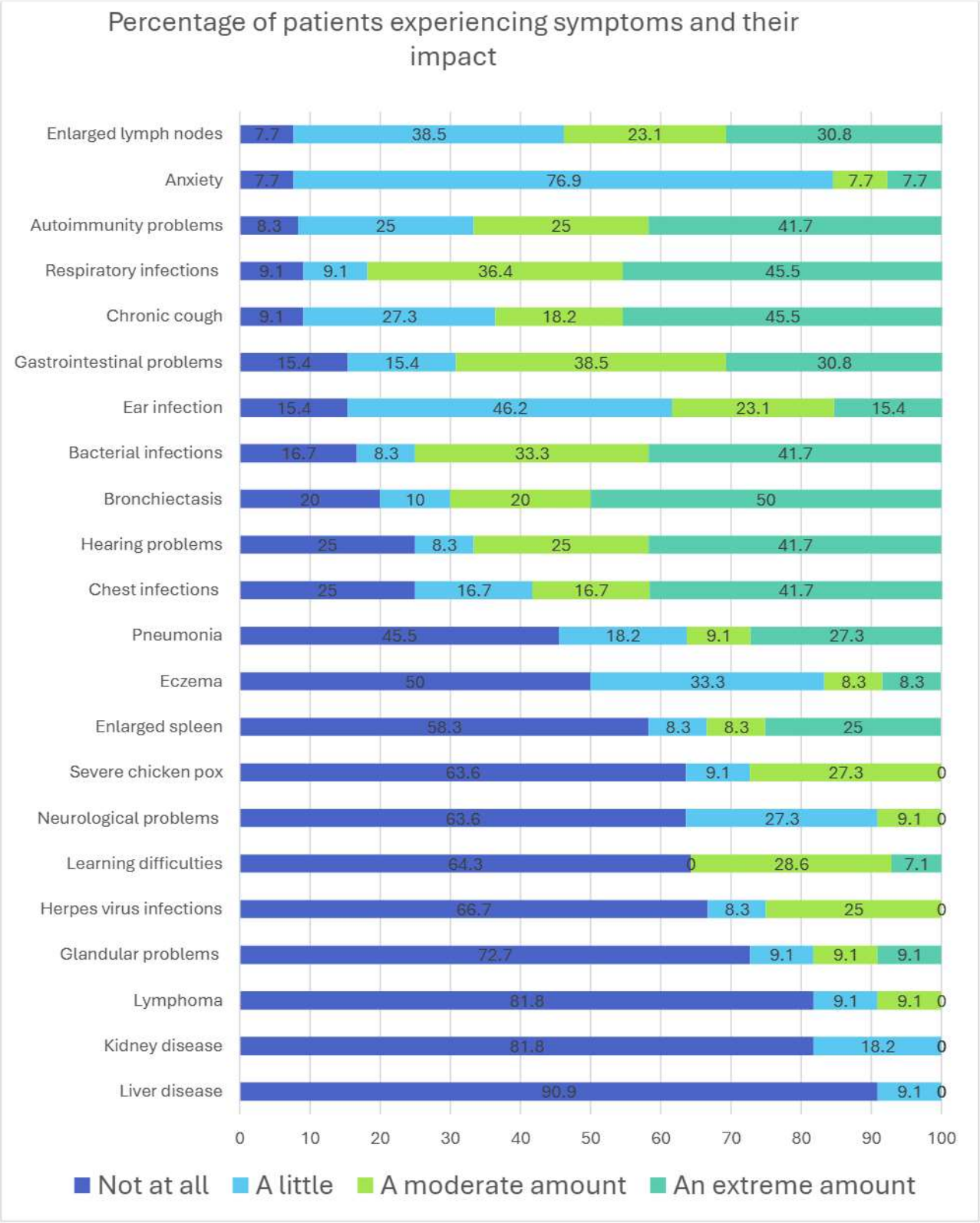
"Not particularly worried just get on with life as best as possible."

- **Quality of life**

Of 13 respondents only 4 reported satisfaction with quality of life.

- **Symptoms experienced when living with APDS and their impact**

Symptoms which were reported as having an extreme impact were bronchiectasis, respiratory infections, chronic cough, autoimmunity problems, hearing problems, enlarged lymph nodes, gastrointestinal problems and enlarged spleen.



Other symptoms experienced were:

Sinus, kidney pains, bad back, shingles, vertigo spinning head, dizziness, rhinitis, weak bladder(incontinence) due to coughing, vomiting and nausea, holes in ears due to frequent ear infections, enlarged tonsils obstructing airways, causing difficulty to eat and sleep.

- **Impact of living with APDS and on family life**

Of the eight respondents, seven felt APDS highly affected their family and one moderately.

On living with APDS

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

"[Patient] has had a long and hard journey to get her diagnosis. It has had a big impact on our family and our relationships with doctors. For 7 years nobody believed anything was wrong with [patient}. On the face of it [the patient] looks like a healthy 8 year old, but [the patient] has struggled with adjusting to life when infections hit. [Patient] loves school and would often get anxiety about returning to school after being off for so long. It also affected me as a mother as I knew something was wrong but was unable to get the help we needed as nobody knew how to help."

"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, etc."

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

"getting infections and hospital admissions." *"Stressful. Requires a lot of patience."*

"Challenging not having a lot of answers."

"We as a family with APDS and 4 of us has issues we just got on with life."

"Short stature incurs teasing and unable to partake in lots of activities. Holes in ears prevent water sports and also hair washing is problematic."

"It's a medicalised life with regular blood tests, regular immunoglobulins replacement therapy."

"Mindful of no soft plays, limit to parks and long walks."

Impact of APDS on family life:

"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."

"Unable to work and socialise. Tired and lack of sleep. Difficult to maintain routine."

"Disproportionately caring for child with APDS over other children, lots of holiday from work spent hospital admissions, days work around physio /. "

"Restricted activities." "its stressful."

"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."

"Before diagnosis, we spend 5 years of month after month being an in patient. Every month on antibiotics for 5 years. Couldn't eat due to in large tonsils causing him to bring his food up after every meal and chocking when sleeping. Couldn't go for wet weather walks (which we can now) however still can't walk far distances."

- **Burden of treatment**

All 14 respondents reported they/the patient were currently taking medication (Table 2). The profile and number of medications taken to manage APDS varied for each respondent. Medication included immunoglobulin therapy (N=12), prophylactic antibiotics (N=9), immunosuppressants (N=6), prophylactic antivirals (N=5), Sirolimus (N=3), Leniolisib (N=6). Two respondents were taking six medications, with two others reporting taking 4-5 medications to manage APDS.

Table 2: Medications taken

Respondent	Antibiotics	IG therapy	Immuno-suppressant	Antivirals	Sirolimus	Leniolisib
1						
2						
3						For 1 month only
4						
5						
6						
7						
8						
9						Unsure
10						
11						
12						
13						
14						

- **Impact of disease burden on patients and the NHS**

Table 3, below, summarises the number of outpatient, inpatient and days spent in hospital over the last 12 months, as reported by 13 respondents. This varied considerably between respondents.

The overall findings underline the impact on individuals and families in terms of time spent in managing appointments and disruption to their lives by time spent in hospital. The results also indicated a significant healthcare burden to the NHS.

Table 3: Number if outpatient/inpatient and days in hospital

Respondent	Outpatient visits	Inpatient visits	Days in hospital
1	2	0	0
3	16	6	14
4	>20	6	80
5	>200	0	0
6	8	4	30
7	10	0	20
8	0	1	10
9	2	0	0
10	12	42	42
11	12	1	2
12	18	2	4
13	6	0	6
14	14	5	21
Totals	**320+**	**67**	**229**

- **Help with personal care**

Of eleven respondents, three required help with personal care. One of the respondents was a carer for a 14-year-old, and two responders were family members or friends of the patient who was three years old. Personal care included washing (N=3), going to the toilet (N=2), cooking (N=1), mobility (N=1), and administering medication (N=1).

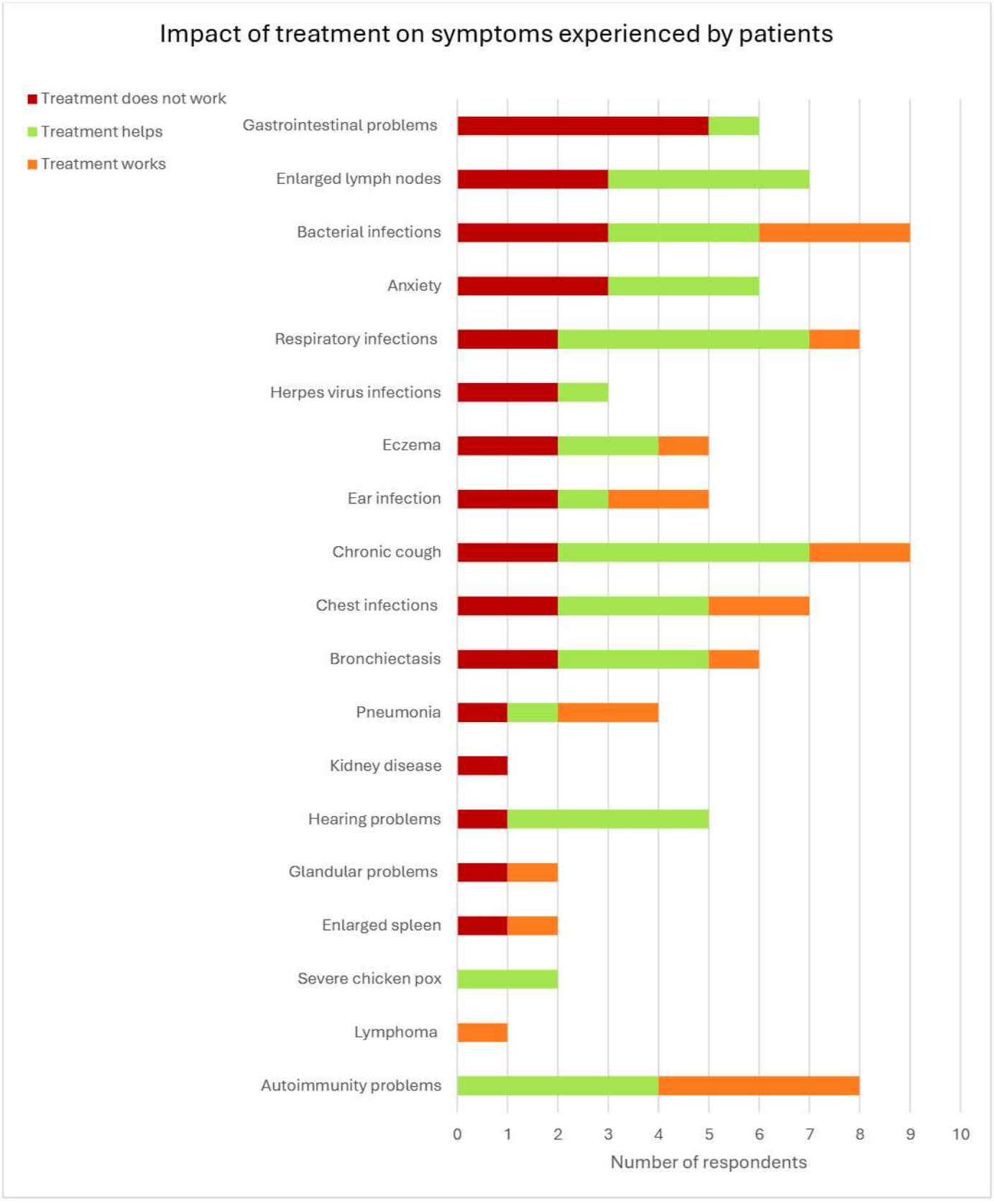
Carers of affected children reported:

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

"2-3 physio sessions a day, medicine administered daily, weekly subq infusions, frequent soiling as on antibiotics regularly."

"Cooking the meals, shower and sometimes mobility assistance."

- **Symptoms not addressed by current treatments – unmet need**



- **Use of Leniolisib for APDS: side effects, benefits, support for access**

Six of 14 respondents had been treated with Leniolisib, with one respondent saying they were unsure (Table 2).

Three of five respondents had experienced side effects from using Leniolisib. One respondent reported a headache, one respondent reported fatigue and diarrhoea, and one respondent reported mouth ulcers and eye infections.

Benefits of Leniolisib

Of the six respondents who had been treated Leniolisib, five reported benefits of Leniolisib. This included a reduction in antibiotic use (N=2), bring bloods [blood count] up (N=1), increasing energy and appetite (N=2) and reducing coughing (N=1), hospital admissions (N=1) and reduced lymph nodes (N=1).

One respondent did not report any benefits as they had only taken the treatment for one month so were yet to find out.

Benefits noted:

"Reduced coughing, reduced the amount of need of antibiotics."

"it has brought his bloods up."

"Reduced lymph nodes. More appetite and energy."

"Increased energy and appetite."

"[Patient] had been on antibiotics for 5 years with serval Hospital additions where so as starting treatment to date of 8 months [Patient] has only had 3 antibiotics and no Hospital additions."

"I would recommend everyone with Apds try this treatment as I have noticed improvement slightly in my condition which has made me feel a little better."

Support for Leniolisib as a treatment option

Of the eight respondents to this question, all eight would recommend Leniolisib.

"100% would recommend the medication. As a parent you want what is best for your children, just having the chance to try a medication for a condition of this nature gives us just that little bit of hope that [patient] will one day be healthier then what [patient] is today and for that reason I would always recommend it."

Drawbacks

Of the six respondents who had been treated Leniolisib, three reported drawbacks. This included the possible side effects listed (N=1), having mouth and tongue ulcers for the first time (N=1), and Leniolisib not tackling the infection damage that was caused before starting the Leniosilib (N=1).

Patients who might benefit more, or less, from Leniolisib

Of the five respondents to this question, all five reported they thought everyone should have access to the treatment. One respondent identified patients who are unable for other treatments would benefit more from the treatment:

"[patient] is unable to have a bone marrow transplant due to [their] 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."

Dated 16th August 2024.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

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

NHS organisation submission (CCG and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHSE CRG
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for a CCG or NHS England in general? Yes Commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? Yes An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHSE CRG – a Lead and Inform CRG which is NHS funded (professional members are NHS staff, the core administration team are NHSE employees).
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is no national guidance for the treatment of APDS.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway to diagnosis is well defined. This is a rare immunologic disorder and patients will be under the care of a paediatric or adult immunodeficiency service. The approaches to treatment depend on the clinical features and vary from supportive only with prophylaxis with antimicrobials, immunoglobulin replacement and surveillance for lymphoreticular malignancy the risk of which is very high in this patient group (14% in the most recent European series) and higher than in similar disorders of immune dysregulation. Given the high rate of infection, immune cytopenias, lymphoma, bronchiectasis and solid organ malignancy in this disorder some patients are offered pre-emptive haematopoietic stem cell transplant. The lymphadenopathy and splenomegaly and cytopenias are currently treated with mTOR inhibitors. There is no significant variation in approach between physicians across the NHS. This is a rare condition that is usually treated collaboratively between centres with shared expertise.
8. What impact would the technology have on the current pathway of care?	At the moment off-label use of mTOR inhibitors are employed for these patients and this does impact some facets of disease. For those considered for haematopoietic stem cell transplant the nature of the gain of function mutations makes a non-myeloablative approach (reduced intensity conditioning – RIC) as employed in most primary immunodeficiency (PID) a challenge, because loss of engraftment due to survival advantage of the recipient cells is frequently seen requiring then more than one HSCT. This targeted treatment, the first available for this disorder may offer a cleaner than mTOR option and if this also reduced the lymphoma and solid organ malignancy risk by affecting all nucleated cells this would potentially offer a simpler and less risky regimen.

The use of the technology

9. To what extent and in which population(s) is the technology being	This new therapy would only be suitable for patients with APDS1 of which there are thought to be 27-35 prevalent patients currently in the whole of the UK. It is not in use currently.

used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The medication would be used to replace mTOR inhibitors and in good responders might displace the need for HSCT.
10a. How does healthcare resource use differ between the technology and current care?	The long term healthcare resource in a good responder may decrease both in acute and non-acute attendance at hospital, reducing OPA and acute service utilisation, but also in those with normalisation of immune parameters the need for ongoing IgG replacement may stop. At present the treatments are lifelong (apart from HSCT) and the tendency is to worsening clinical status with accumulating co-moribidity over time. This medicine would in theory provide the opposite long term outcomes with improved health and improved quality of life rather than progressive deterioration.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This would only be prescribed from accredited specialised immunology services (paediatric and adult).
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Pharmacy for dispensing, potentially homecare delivery of the medication for community dispensing. The other patient monitoring and infrastructure would not change or utilisation is predicted to reduce.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The testing already undertaken (genetic confirmation of ADPS1) is already part of standard of care and routinely commissioned in the NHS for appropriate specialist centres (Pi3K genetics are on the Genomics England R15 panel).

11. What is the outcome of any evaluations or audits of the use of the technology?	Future audit would be QoL, resolution of cytopenias, resolution of lymphadenopathy/splenomegaly, reduction in infection and associated healthcare resource utilisation, reduction in lymphoma rate.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not known but this disorder is autosomal affecting male and female sex equally, there is no ethnic restriction – has been seen in most ethnicities so far in the limited number of worldwide patients.
12b. Consider whether these issues are different from issues with current care and why.	This does not differ from current care, although it should be noted that for those patients being considered for HSCT the availability of suitable donors in individuals from some ethnic minority backgrounds precludes access to current standard of care for some individuals.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE 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]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for your response is **5pm** on **Friday 4 October.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

Part 1: Treating activated phosphoinositide 3-kinase delta syndrome and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Austen Worth
2. Name of organisation	Great Ormond Street Hospital for Children Foundation NHS Trust
3. Job title or position	Consultant in Paediatric Immunology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with activated phosphoinositide 3-kinase delta syndrome ? ☒ A specialist in the clinical evidence base for activated phosphoinositide 3-kinase delta syndrome or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I am principal investigator and lead for the only UK study site for the study "An Open-label, Single Arm Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Leniolisib in Pediatric Patients (Aged 1 to 6

	Years) with APDS (Activated Phosphoinositide 3-Kinase Delta Syndrome) Followed by an Open-label Long-term Extension"
8. What is the main aim of treatment for activated phosphoinositide 3-kinase delta syndrome? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The primary aim of treatment in activated phosphoinositide 3-kinase delta syndrome (APDS) is to stabilise the existing disease complications and prevent progression (recurrent infections, bronchiectasis, enteropathy, lymphoproliferatation and widespread autoimmunity). Secondary aims of care are 1. to improve the quality of life of patients and minimise their medical interventions in everyday life, 2. detect any malignancy (or pre malignancy assoicated with Epstein Barr Virus (EBV) infection) at an early to allow optimal and early treatment, 3. To optimise the clinical condition of patients to allow the best possible outcome forearm potentially curative haematopoietic stem-cell transplant. 4. To facilitate patient choice in treatment options, between aggressive supportive care and haematopoietic stem-cell transplant.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	• Reduction in infection frequency, as demonstrated by reduced antibiotic use • Lack of progression of chronic lung disease (as determined by chest CT findings, lung function testing and real world patient functionality) • Lack of development of new autoimmune autoinflammatory complications • Reduction in lymphoproliferative Asian (lymph node size, spleen size) • Reduced hospital admissions • Control of an existing EBV infection (as determined by viral detection by PCR in peripheral blood) • Improvement in specific blood parameters (full blood count, immunoglobulin levels, proportion of naive T-cells, differentiation pattern of B-cells) • Ability to make functional antibody responses and cessation of immunoglobulin replacement therapy • Improved quality of life (as measured by school attendance, employment, psychological wellbeing, normality of life)
10. In your view, is there an unmet need for patients and healthcare professionals in activated phosphoinositide 3-kinase delta syndrome ?	Yes

11. How is activated phosphoinositide 3-kinase delta syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently APDS is treated by specialist immunology services by; 1. Close monitoring teams expert in this condition 2. Aggressive conservative management 3. Haematopoietic stem-cell transplant (HSCT) for selected patients. Aggressive conservative management may include some or all of the following; 1. Regular outpatient appointments at specialist immunology services 2. Immunoglobulin replacement therapy 3. Antimicrobial prophylaxis 4. Early access to treatment courses of antimicrobials during infections 5. Regular planned in-patient hospital stays with intensive physiotherapy and intravenous antibiotics for those patients with severe established bronchiectasis 6. Assessment and treatment of inflammatory and autoimmune complications. This may include inpatient stays for diagnostic workup, endoscopies, bronchoscopies, specialist blood tests, extensive radiological investigations 7. Treatment with immunosuppressive medication (including corticosteroids, sirolimus, monoclonal antibody therapy) 8. Nutritional support 9. Management of atopy 10. Early treatment of EBV infection which may include rituximab 11. Psychological support appropriate for patients with serious chronic medical problems 12. Holistic support to facilitate age-appropriate education and employment Haematopoietic stem-cell transplant is provided by a small number of commissioned specialist treatment centres (paediatric and adult). Decision on progression to transplant is agreed at regional or national multidisciplinary team

	meetings. Support around decision-making is provided by an active international network of immunodeficiency and specialist transplant expert. The largest published cohort of APDS patients treated by HSCT, had an 86% 2 years survival, but a high level of graft rejection and a 68% transplant cure rate at 2 years. Many of those patients who underwent graft rejection required a second haematopoietic stem-cell transplant. Treatment is based on extrapolation from other combined immunodeficiency forward/antibody deficiency disorders, and from published studies. National UK treatment guidelines endorsed by a professional body do not exist. Care is provided by specialist immunology centres (paediatric or adult). Assurance of quality of care is provided through regional immunology clinical network meetings, national forward/regional MDT's (e.g. Adult CVID MDT, immunodeficiency HSCT MDT, Paediatric HSCT national audit meeting), national and international meetings and conferences (clinical immunology professional network annual meeting (BSI-CIPN), European Society of Immunodeficiency (ESID), european Bone Marrow Transplant Inborn Errors Working Group (EBMT-IEWP)). Leniolisib treatment would be provided under specialist immunology expertise, and would not impact on where patients are treated. Leniolisib use may change the pattern of referral of patients with APDS to haematopoietic stem-cell transplant (potential avoidance of HSCT, HSCT performed in healthier patients with better outcomes, HSCT availability for more patients) although this is difficult to predict and would need close monitoring.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Leniolisib is an oral medication which can be safely administered to patients as outpatients. Blood tests to monitor for potential side-effects will need to be taken regularly, however these would occur at the same frequency as regular monitoring blood tests which would be needed for routine clinical care anyway. Some additional monitoring blood tests may be required immediately after

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	starting the medication. These blood tests are standard routine investigations (full blood count, renal function, liver function). Further radiological imaging may be requested to measure the response to treatment and determine whether ongoing treatment is appropriate. Leniolisib would be prescribed in tertiary care, however monitoring blood tests would be provided by primary or secondary care. This would be the same as current clinical care arrangements.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Current published results for the use of Leniolisib in APDS are for relatively small numbers of patients, and the maximum published follow-up time is approximately 7 years since starting Leniolisib. This relatively limited data is as a consequence of recent discovery of this condition, and its rarity. Although data on long term impact of Leniolisib in patients with APDS is limited, in my opinion, based on published literature and experience of using linear loose hip both on a compassionate access basis and within a clinical trial (in children), I feel it is extremely likely that Leniolisib will both increase the quality of life and duration of life for patients with APDS
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The majority of symptomatic patients with APDS are likely to gain some benefit from Leniolisib. We have insufficient data at present to no whether there may be some treatment refractory patients within this cohort. The patients who stand to gain the most benefit from this treatment are; • Patients with early disease which has not yet progressed to end organ damage (e.g. bronchiectasis, chronic liver disease, interstitial lung disease, lymphoma). Treatment with Leniolisib is likely to prevent or slow the development of these complications, resulting in better overall quality of life and function.

	• Patients who wish to proceed to haematopoietic stem-cell transplant will have their clinical condition optimised by treatment with Leniolisib in the months or years prior to HSCT. This will result in better outcomes from HSCT, and less long term complications and morbidity post HSCT • Some patients may have to severe disease for HSCT to be considered an appropriate treatment options. Leniolisib may improve the clinical condition of these patients allowing HSCT to be a realistic curative treatment options.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Treatment with Leniolisib will have minimal impact on current care for patients with APDS. Published data suggests that it will reduce healthcare costs and contact with healthcare professionals.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients would need to have genetically proven APDS1 or APDS2 to be eligible for Leniolisib treatment. In selected patients where pathogenicity of genetic variants is not proven, a specialist functional immunology investigations may be required to prove pathogenicity. This is currently available on a research and development basis at individual NHS clinical immunology laboratories.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	I think it is extremely likely that the majority of APDS patients treated with Leniolisib will have an improvement in their QALY assessment. Potential missed benefits may include use of NHS resources, educational attainment an outcome , social integration and psychological wellbeing. For example in patients who able to come off immunoglobulin replacement therapy, this result in fewer hospital day case admissions, fewer monitoring

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	blood tests, less psychological impact of parents having to insert needles into their children on a weekly basis.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Leniolisib is a targeted therapy APDS, and early data suggests that it can result in a sustained modification (improvement) in patients immune function. This significantly improves patient choice in their long term treatment, particularly around the appropriateness , timing an outcome from a potentially curative HSCT. For patients with more severe disease, Leniolisib may open up the possibility of a curative HSCT, which would not be otherwise offered due to very high risk of mortality.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Generally significant side-effects have only been reported at low frequency with Leniolisib and overall studies assessing safety have demonstrated a reduction in symptomatology for patients taking Leniolisib. More serious adverse reactions (e.g. Severe skin rashes) have been reversible when the treatment has stopped. Overall I do not feel that adverse reactions will impact on the management of patients or their quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Entrance criteria the published clinical trials for Leniolisib in APDS have been based on measurable enlarged lymph nodes. This has allowed an objective measure of response to treatment. This does not reflect the real world indication for wanting to start treatment, and therefore there may be some differences between the trial treated population, and patients who would be treated in real life experience. Nonetheless the secondary outcome measures reported in clinical trials are much more clinically relevant and these are also positive for treated patients.

	Although initial outcome data seems very positive and the functional immunology recovery following initiation of Leniolisib predicts a better long term outcome, we do not yet have significant long term data beyond 5 years of treatment. Although short term adverse reactions associated with Leniolisib are acceptable considering the severity of the condition, we do not yet have sufficient data on potential long term adverse reactions associated with Leniolisib (such as risk of malignancy). Given the severity of the underlying condition and the current published safety data, however, I feel it is unlikely that any long term adverse events would result in a higher incidence of serious medical complications than dosing with existing conservative management. HSCT as an alternative curative therapy is also associated with long term mortality and morbidity, and there is no published data on long term outcome measures beyond 2 years post HSCT
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Data from the early access programme forward/compassionate use. This data is held by Pharming, although some limited cohort data has recently been presented at a conference (not peer reviewed)
22. How do data on real-world experience compare with the trial data?	There is insufficient real world experience currently available.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	As this nice proposal is only considering patients aged 12 and above, approval will lead to in equity of care for children under the age of 12. This group of patients are some of those likely to gain most benefit from treatment with Leniolisib, as treatment could be established before the development of bronchiectasis and prevent chronic lung disease and lifelong medical complications. Given the rarity of this condition and the challenges associated with running clinical trials in younger children, the trials for younger age groups are delayed and ongoing. Treatment of patients under the age of 12 will therefore need to

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	continue to be provided via the early access scheme, and therefore reliant on the compassionate access provided by Pharming. I am not aware of any other potential equity of access issues relating to Leniolisib, and being an oral medication which can be taken at home, this treatment will potentially i disproportionately benefit those patients with impaired access to healthcare services.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Leniolisib is very likely to improve the clinical outcomes and quality of life for the majority of patients with APDS

Healthcare costs and burden of care for the majority of patients will be reduced

Treatment with Leniolisib will increase and improve patient choice around long term treatment options such as haematopoietic stem-cell transplant

Published data suggests a selection of patients may be able to come off immunoglobulin replacement therapy which would have significant benefits to patient quality of life and drug costs

Use of Leniolisib in conjunction with existing treatment options is extremely likely to improve patient's survival

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NICE 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]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for your response is **5pm** on **Friday 4 October.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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We reserve the right to summarise and edit comments received, 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 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.

Part 1: Treating activated phosphoinositide 3-kinase delta syndrome and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Siobhan Burns
2. Name of organisation	University College London
3. Job title or position	Professor of Translational Immunology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with activated phosphoinositide 3-kinase delta syndrome ? ☐ A specialist in the clinical evidence base for activated phosphoinositide 3-kinase delta syndrome or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for activated phosphoinositide 3-kinase delta syndrome? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve/treat symptoms and disease complications and prevent progression.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Ant of the following: reduction in lymphadenopathy and splenomegaly, amelioration/prevention of autoimmune/inflammatory complications, improvement in infection frequency, improvement in B-cell function as evidenced by the ability to reduce/discontinue immunoglobulin therapy, prevention of lymphoma
10. In your view, is there an unmet need for patients and healthcare professionals in activated phosphoinositide 3-kinase delta syndrome ?	Yes- there are no pathway-specific treatments aimed at restoring function of the dysregulated signalling pathway in immune cells. Therefore, immune-modulatory therapy is generic and particularly in the case of immunosuppression (for example with corticosteroid use) can cause unwanted adverse effects.
11. How is activated phosphoinositide 3-kinase delta syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The main principles are infection prevention (using prophylactic antibiotics and /or immunoglobulin replacement therapy) and management of disease complications. In particular, inflammatory/autoimmune complications are typically managed with immunosuppressive therapies. No agreed clinical guidelines are in place for this internationally and a range of different immunosuppressive agents are used (eg steroids, mycophenolate mofetil, mTOR inhibitors). Malignancy (usually lymphoma) is managed with standard chemotherapy protocols. Allogenic haematopoietic stem cell transplant (allo-HSCT) is a potential curative treatment, albeit with significant risks. There is no agreed pathway of care and while practice around prevention of infections is relatively standard, other management choices are variable. Leniolisib would provide a targeted therapy aimed at correcting the aberrant signalling pathway which (i) would provide a more specific form of immune modulation with fewer reported side effects that other immunosuppressive agents and (ii) is likely to reduce infection risk through improvement in immune function.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Leniolisib would in some cases be used in addition to current care – for example where a patient is only on infection prophylaxis treatment- and in some cases in the same way as current care – for example other immunosuppressive agents could be switched to leniolisib for management of inflammatory/autoimmune complications. My view is that leniolisib should only be used in a specialist clinic by physicians who are appropriately experienced to manage APDS. Training for medical staff, pharmacists and clinical nurse specialists may be required. Drug monitoring blood tests (all routinely available in current pathology laboratories).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect the technology to improve health- related quality of life and length of life by improving immune function, reducing infections and improving/preventing autoimmune/inflammatory complications. There is also growing evidence that controlling inflammatory complications will improve allo-HSCT outcomes including transplant related mortality.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes- patients with activated PI3-kinase delta syndrome (APDS 1 or 2)
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	For healthcare professionals, this will not be more or less difficult that current care options with a couple of exceptional circumstances: (i) If a patient is able to stop immunoglobulin replacement due to immunological recovery on leniolisib, prescribing oral medications would be easier than arranging immunoglobulin replacement therapy (ii) If leniolisib is sufficiently effective to prevent the need for allogeneic HSCT then it would be significantly easier for treatment.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I am not sure about this. In practice in Primary Immunodeficiency (PID), similar medications are typically started if the patient has clinical symptoms or disease features that suggest they would benefit from treatment. This is decided on a patient-by-patient basis as the clinical phenotype and progression of disease is variable for many PID including APDS. Typically, similar drugs are discontinues in PID if they are not tolerated, the patient chooses not to continue or is poorly compliant, they do not confer benefit or control disease so that a different treatment modality is attempted. Additional blood monitoring tests would be required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes if patients are able to stop immunoglobulin infusions or avoid allo-HSCT.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, as this is a pathway- specific drug for APDS and acts directly to impact the dysregulated immune signalling pathway and therefore restore immune cell function by reversing the effect of the genetic mutation. There are no similar alternatives and therefore this does address an unmet need. Trial data suggests that some patients may be able to stop immunoglobulin therapy due to restoration of antibody production. This would be significant impact on health-related benefit.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In trials so far the drug appears to be well tolerated. For patients where this is not the case, I expect that the drug would be stopped with reversion to currently available treatments.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes In my view the most important outcomes are reduction in immune-dysregulation as evidenced by reduced lymphadenopathy and splenomegaly and the potential for improved antibody production which allowed some patients to stop immunoglobulin therapy – both reported in the trials. Another very important outcome, not addressed in trials, is anecdotal evidence that for PID with significant inflammation (such as APDS), control of immune dysregulation with pathway-specific drugs improves the outcome of HACT. Potential impact to prevent development of lymphoma will need longer experience with using this technology.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	I am not sure as few colleagues in the UK are in practice using the technology (through the early access program) and I have not seen (m)any presentations about real world data in international conferences.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Individuals living in areas not served by a specialist immunology service or for groups where referral to specialist services occur less frequently.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Leniolisib is the only targeted pathway-specific drug with systemic effect available for patients with APDS.
Trial data demonstrates that the drug is well tolerated and effective to reduce immune dysregulation and improve immune deficiency for APDS.
Availability of this drug is expected to improve health outcomes and quality of life for patients with APDS.
There is also potential benefit for APDS patients planning allo-HSC, to improve outcomes
Some longer term benefits (eg impact on lymphoma development and need for allo-HSCT) may not be captured by current data which covers a relatively short use of the drug.

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

Evidence Assessment Group Report

Produced by Newcastle University

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Nicole O'Connor and Fiona Beyer acted as lead effectiveness reviewers.
Cristina Fernandez-Garcia acted as lead health economist.
Sonia Garcia Gonzalez-Moral acted as lead reviewer of the literature search methods.
Sola Akinbolade and Ayomikun Ogunyemi acted as effectiveness reviewers.
Hangjian Wu acted as a health economics reviewer.
Oleta Williams reviewed the literature search methods.

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Report key: [redacted]

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Abbreviations

AE	Adverse events
AIC	Akaike's Information Criterion
APDS	Activated PI3K delta syndrome
BI	Budget impact
BIC	Bayesian information criterion
BID	Bis in die (Twice a day)
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CfB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Company's submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAP	Early Access Programme
EQ-5D	European Quality of Life-5 Dimensions
FAD	Final appraisal document
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
HSUV	Health state utility value
HST	Highly Specialised Technology
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost-effectiveness ratio
IgM	Immunoglobulin
IPTW	Inverse probability of treatment weighting
IRT	Immunoglobulin replacement therapy
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LY	Life year
MAIC	Matching-adjusted indirect comparison
MCS	Mental component summary score (SF-36)
MeSH	Medical subject headings
MTA	Multiple Technology Appraisal
MTC	Mixed treatment comparison
mTOR	Mammalian target of rapamycin
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PFS	Progression-free survival
PfC	Point for Clarification
PCM	Physical component summary (SF-36)
PI3Kδ	Phosphoinositide 3-Kinase delta

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PtGA	Patient Global Assessment
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36
SLR	Systematic literature review
SoC	Standard of care
SPD	Sum of the products of two largest perpendicular diameters of lesions
STA	Single Technology Appraisal
TA	Technology Assessment
TEAE	Treatment emergent adverse events
TTO	Time trade-off
TTOT	Time-to-off treatment
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 presents the model outcomes. Section 1.3 summarises all key issues identified by the EAG relating to clinical effectiveness and cost-effectiveness. Section 1.4 summarises the EAG's preferred assumptions and ICERs.

Further detail regarding key and non-key issues are described in the main EAG Report (Sections 3 to 7).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1: Summary of EAG's key issues

Issue number	Brief summary of issue	Report section(s)
1	The comparator arm used in the pivotal, phase III, randomised controlled trial (2201 Part II) lacks generalisability to current clinical management in the UK.	Section 4.2.2.1
2	Using a discount rate of 1.5% to the QALY gains.	Section 5.2.2
3	In the probabilistic sensitivity analysis, where uncertainty information was not available, the company assumed standard error to be 10% of its mean for parameters.	Section 5.2.3
4	Assumption that the effect of leniolisib treatment will not wane throughout the lifetime of patients.	Section 5.2.4
5	Additional utility gain from the emotional benefit of leniolisib included in the model.	Section 5.2.6
Abbreviations: EAG = Evidence Assessment Group; QALY = Quality-adjusted life year		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the incidence and prevalence of manifestations for APDS, which in turn reduces quality of life decrements experienced by patients receiving leniolisib compared to those under current clinical management.
- Treatment discontinuation leads to increased incidence rates of manifestations associated with APDS, returning to rates experienced under current clinical management. Therefore, treatment discontinuation is an important driver of differences in quality of life.

Overall, the technology is modelled to affect costs by:

- Leniolisib costs: treatment costs for leniolisib with a patient access scheme (PAS) are the biggest contributor to the difference in costs between the leniolisib and current clinical management groups.
- Reduced treatment and monitoring costs of manifestations for APDS: the cost associated with immunoglobulin replacement therapy (IRT), HSCT costs, Immunosuppressant costs and tonsillectomy costs are all higher for patients receiving current clinical management than patients treated with leniolisib (including the cost of leniolisib with a PAS itself)
- Treatment discontinuation: discontinuation from leniolisib treatment reduces costs for leniolisib, increases incidence rates for manifestations (implying increased treatment use associated with various manifestations).

The modelling assumptions that have the greatest effect on the ICER are:

- Discount rate: the company used a 1.5% discount rate for health effects and 3.5% discount rate for costs. Using a 3.5% discount rate to both costs and health effects, as per NICE health technology evaluations (HTE) manual,[1] has a large impact on the ICER.
- QALY gains weight: the company applied a decision maker modifier (1.5 QALY) weight to the incremental QALYs accrued by the leniolisib group in the base-case economic analysis. Removing the QALY gains weight has a large impact on the ICER.
- Treatment waning: the company assumed that there is no loss in the efficacy of treatment in the economic model. The impact of treatment waning can be seen as analogous to treatment discontinuation for part of the cohort. The EAG note that the effect of treatment waning on the ICER can be crudely explored by varying the discontinuation rate. The EAG found that incorporating treatment waning through an increase in the discontinuation rate has a large impact on the ICER.
- Additional utility gain from the emotional impact of leniolisib: the company applied an additional 0.1 utility gain to the leniolisib arm to include the benefit from reduced emotional burden due to the lower expected risk of developing various manifestations and mortality. The EAG found that removing this utility gain has a large impact on the ICER.

1.3 Description of the EAG's key clinical and economic issues

Table 2: Uncertainties in clinical evidence relating to Study 2201 Part II (RCT)

Report section	4.2.2.1
Description of issue and why the EAG has identified it as important	The EAG considers the lack of an active comparator arm in 2201 Part II as a key issue in the clinical evidence. The RCT comparator arm received placebo plus selected concomitant treatments. In the UK, immunosuppressive medications, specifically mTOR inhibitors and rituximab, are part of current clinical management for APDS.Patients with prior use of certain immunosuppressive medications were required to complete a protocol-defined washout period to be eligible for enrolment. More importantly, concurrent use of certain immunosuppressive medications was excluded from the clinical trials, due to potential increased risk of infections. This exclusion raises concerns about the generalisability of the comparator. Additionally, baseline imbalances, novelty of the surrogate primary endpoints, and a small sample size used in the analysis introduce uncertainties in the true magnitude of effect, warranting cautious interpretation of the results.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Inputs to the economic model based on the RCT may overestimate the cost-effectiveness of the technology as the comparator group in the study differs from the current clinical management group included in the model.
What additional evidence or analyses might help to resolve this key issue?	The company provided an indirect treatment comparison that used patient data from the ESID registry as a control arm; their care likely better reflects standard care. Therefore concerns about generalisability are partially addressed by this additional evidence.
Abbreviations: EAG = Evidence Assessment Group; APDS = Activated phosphoinositide 3-kinase delta syndrome; mTOR = mammalian target of rapamycin; RCT = randomised controlled trial.	

Table 3: Key issue - 1.5% discount rate applied to future QALYs

Report section	5.2.2.3
Description of issue and why the EAG has identified it as important	The company has applied a discount rate of 1.5% to future QALYs. However, the EAG consider this to be a deviation from the NICE reference case.[2] The EAG believe that this deviation is insufficiently justified and does not meet the NICE reference case criteria: 1) The technology is for people who would otherwise die or have a very severely impaired life; 2) It is likely to restore them to full or near-full health; 3) The benefits are likely to be sustained over a very long period.[1]
What alternative approach has the EAG suggested?	The EAG suggest that the base-case analysis includes a discount rate of 3.5% for both costs and health effects as per the NICE reference case. A sensitivity analysis incorporating a 1.5% discount rate applied to future costs and effects has been included for consideration by the committee.
What is the expected effect on the cost effectiveness estimates?	The use of the reference case discount rate to both costs and effects will increase the ICER reducing the cost-effectiveness of leniolisib compared with current clinical management.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow up data would provide the necessary evidence needed to assess whether the criteria set by NICE for the application of the 1.5% discount rate are fully met.
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year	

Table 4: Key issue - standard error to be 10% of its mean for parameters where uncertainty information was not available

Report section	5.2.3.2
Description of issue and why the EAG has identified it as important	In the probabilistic sensitivity analysis, the company assumed the standard error (SE) to be 10% of its mean for parameters where uncertainty information was not available, which applies to most of the input parameters in the economic model. A review of previous NICE technology appraisals found that most models typically assumed SEs between 10-30% of the mean (20% was most common) for such parameters.[3] Therefore, in the EAG's view, the rationale for assuming an SE 10% of the mean was insufficiently justified.
What alternative approach has the EAG suggested?	The EAG suggested using a more a conservative value (i.e., an SE that is 20% of the mean) in the probabilistic sensitivity analysis where uncertainty information was unavailable or there was insufficient evidence.
What is the expected effect on the cost effectiveness estimates?	The use of a 20% SE for parameters where uncertainty information was not available implies that a more conservative approach to characterising uncertainty is taken. There is no expectation that the ICER will change in a specific direction.
What additional evidence or analyses might help to resolve this key issue?	In the future, further information about the level of uncertainty around key input parameters (such as treatment effectiveness and utilities) can be obtained through clinical trials, observational data or clinical expert opinion.
Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; HST = Highly Specialised Technology; ICER = Incremental Cost-Effectiveness Ratio; SE = Standard Error	

Table 5: Key issue - assumption that the effect of leniolisib treatment will not wane throughout the lifetime of patients

Report section	5.2.4.1
Description of issue and why the EAG has identified it as important	The company has stated that the benefits of leniolisib are expected to be sustained during the lifetime of patients. Hence, an assumption of no loss in efficacy has been incorporated in the economic model. This assumption is based on available follow-up data for up to six years. The EAG note that there is no published evidence that the efficacy of leniolisib will continue beyond 6 years.
What alternative approach has the EAG suggested?	The EAG acknowledge there are several different potential approaches, each with their own associated difficulties, that could be taken to incorporate a treatment waning effect into the company's model. The EAG have chosen to adjust the model's discontinuation rate to incorporate the possibility of treatment waning. The EAG propose that the mean discontinuation rate derived from the company's own Expert Consultancy project is applied to the base-case analysis. Further testing of potential efficacy waning was also explored in the EAG sensitivity analyses. The EAG acknowledge that this approach has a significant limitation of excluding the cost of leniolisib treatment.
What is the expected effect on the cost effectiveness estimates?	A reduction in the long-term efficacy of leniolisib has the potential to significantly reduce the QALY difference between groups and decrease treatment costs in the leniolisib group.
What additional evidence or analyses might help to resolve this key issue?	Obtaining longer term data is the best way to establish if the efficacy of leniolisib will be sustained.
Abbreviations: EAG = Evidence Assessment Group; QALY = Quality-Adjusted Life Year	

Table 6: Key issue - additional utility gain from the emotional benefit of leniolisib included in the model

Report section	5.2.6.3
Description of issue and why the EAG has identified it as important	The company assumed that APDS patients receiving leniolisib were expected to benefit from reduced emotional burden due to the lower expected risk of developing various manifestations and reduced mortality, and increased hope due to the availability of a new treatment. Therefore, the company applied a further utility gain, in addition to the assumed utility improvements associated with a reduction in rates of manifestations. The EAG note that this assumption has a large impact on the ICER, however the company has not provided sufficient justification regarding the quantification of this additional impact on utility.
What alternative approach has the EAG suggested?	The EAG suggest removing this assumption given its lack of justification.
What is the expected effect on the cost effectiveness estimates?	Removing the utility gain assumption increases the ICER through a decrease in QALYs for the leniolisib arm.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on the impact of utilities for leniolisib patients, due to a reduction in emotional burden, would help to evaluate the validity of this assumption.
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year	

1.4 Summary of the EAG's preferred assumptions and ICER

Table 7: Summary of EAG's preferred assumptions and ICER

Technologies	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
CS base-case – Probabilistic (without QALY gain weight)					
Leniolisib	[redacted]	[redacted]	[redacted]	11.57	[redacted]
SoC	1,613,679	[redacted]			
Fixing errors (1-3) – Probabilistic (without QALY gain weight)					
Leniolisib	[redacted]	[redacted]	[redacted]	11.49	[redacted]
SoC	1,620,167	[redacted]			
EAG base-case – Probabilistic					
Leniolisib	[redacted]	[redacted]	[redacted]	4.51	[redacted]
SoC	1,646,253	[redacted]			
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year; SoC = Standard of Care					

Table 8: Summary of key EAG scenario analysis results – deterministic analysis: leniolisib versus standard or care

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	N/A	[redacted]	3.54	[redacted]
1	Treatment discontinuation rate = 14%	Treatment discontinuation rate = 0%	[redacted]	9.49	[redacted]
2		Treatment discontinuation rate = 10%	[redacted]	4.04	[redacted]
3		Treatment discontinuation rate = 30%	[redacted]	2.80	[redacted]
4	Discount rate = 3.5% for both costs and health effects	Discount rate =1.5% for both costs and health effects	[redacted]	4.62	[redacted]
12	No lower limit on utilities	Lower limit on utilities elicited from TTO tasks	[redacted]	3.12	[redacted]

Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental Cost-ffectiveness Ratio; QALY = Quality-Adjusted Life Year; TTO = Time trade-off

2 PLAIN LANGUAGE SUMMARY

What was the question?

Does the drug leniolisib successfully treat APDS in people aged 12 years and over, and does it provide good value for money to the public?

APDS is a rare genetic disorder caused by an overactive enzyme from a genetic mutation. It affects the production of white blood cells. This leads to frequent infections, lung disease (bronchiectasis), inflammatory bowel disease and increased risk of, malignancies such as lymphomas. In the UK, treatments for APDS are decided on a case-by-case basis and treat the symptoms, not the cause. They may include IRT (immunoglobulin replacement therapy), antimicrobial therapies, immunosuppressive treatments, surgical interventions, and, in severe cases, HSCT (stem cell therapy). Currently, no licenced medicines for APDS are approved by marketing regulators in the UK.

Leniolisib is a drug that has been developed to treat the cause of APDS by fixing the overactive enzyme. This allows white blood cells to develop properly and to fight infection more successfully. It is taken as a tablet twice a day.

What did we do?

This project critiques and summarises the manufacturer's evidence on the clinical and cost-effectiveness of leniolisib for treating APDS in people aged 12 years and older. It focuses on safety (adverse events), efficacy, and value for money. Leniolisib has been tested in 38 people with APDS across three clinical trials, including a 12-week randomised controlled trial in 31 people.

What did we find?

The randomised controlled trial reported improvement in levels of white blood cells for fighting infection and reduction in lymphadenopathy (swelling of lymph nodes), but there are some limitations discussed in the report that should be considered when interpreting the results. The manufacturer conducted an extended trial which is ongoing. So far these positive results are maintained and most adverse effects are mild. The rate of infections and levels of antibodies in the blood (which fight infections) were measured to determine how well leniolisib works outside of a clinical trial setting. An 'indirect treatment comparison' compared infection rates and levels of antibodies in the blood of people taking leniolisib from the extended trial compared to people not taking leniolisib who were in a patient registry. There was an improvement in both measures in both the trial and the indirect treatment comparison. The company presented an economic model which suggested that leniolisib could be cost-effective. A lack of available data made it difficult to be confident about cost-effectiveness. The EAG's own analysis suggest that there is uncertainty about the value for money of leniolisib compared to current clinical management.

3 CRITIQUE OF THE COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Critique of the company definition of the decision problem

A summary of the company's decision problem in relation to the final NICE scope is presented in Table 9 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in section 5.2.1.

Table 9: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with APDS 12 years of age and older	Adults and adolescents with APDS 12 years of age and older	The population is in line with the: participant eligibility criteria for the pivotal leniolisib trials the anticipated licence wording from the Medicines and Healthcare products Regulatory Agency (MHRA), and the population anticipated to receive leniolisib in UK clinical practice	The EAG note a concern with generalisability and a deviation from the decision problem with regards to the starting age in the economic model. Further information is provided in Section 3.1.1.
Intervention	Leniolisib	Leniolisib	N/A – decision problem is aligned with final scope	The intervention is in line with the NICE scope
Comparator(s)	Established clinical management without leniolisib	Established clinical management without leniolisib, specifically covering: antimicrobials, immunoglobulin replacement therapy (IRT), immunosuppressive therapies (including steroids, rituximab and mammalian target of rapamycin [mTOR] inhibitors), haematopoietic stem cell transplantation (HSCT), surgery	N/A – decision problem is aligned with final scope	Overall, the EAG agrees that the company's choice of comparators is appropriate. However, we note an issue about the choice of the comparator used in 2201 Part II and discuss this further

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		and other procedures, in line with current practice in the UK.		in Section 4.2.2 below.
Outcomes	Infections Lung function Fatigue Mortality Disease severity Immunophenotype measures (lymphocyte counts, immunoglobulin levels, cytokine and chemokine levels) Immune system function (lymph node size, spleen and liver volume size, use of IRT) Adverse and serious effects of treatment Health-related quality of life (HRQoL)	Immunophenotype measures (including lymphocyte counts [such as naïve B cells], serum immunoglobulin levels, and cytokine and chemokine levels) Immune dysregulation measures (including lymphoproliferation, lymphadenopathy [lymph node size], splenomegaly [spleen volume/size], cytopenias and gastrointestinal manifestations) Immune deficiency measures (infections, use of IRT and antibiotics, and hearing loss) Lung disease (bronchiectasis-associated airway disease and advanced lung disease) Fatigue Malignancy and mortality Disease severity and HRQoL (SF-36 and PtGA) Adverse and serious effects of treatment	All outcomes requested by NICE in the final scope are presented in the evidence submission. Neither lung disease nor mortality were investigated as pre-specified efficacy outcomes in the clinical trial programme for leniolisib. However, safety data are available from the clinical trials for both outcomes, including reports of respiratory disorders, infective exacerbations of bronchiectasis, and deaths. [4,5] In addition, real-world evidence is available for the impact of leniolisib on lung disease. [6,7] This evidence submission addresses lung disease and mortality in Section B.2.6.4 and Section B.2.6.6, respectively.	The EAG considers the outcomes described in the CS to broadly match the final scope issued by NICE. Additional data was provided for measures not specified in the final NICE scope and these inform the economic model. See section 3.1.2 of the CS for further information.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of	The company states that cost-utility analysis was conducted for leniolisib versus the relevant comparator, established clinical management in the UK. As per	The EAG note that PSS costs were not included in the economic model	Some concerns: The company has confirmed in their (Point for Clarification)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	the NICE reference case, cost-effectiveness was expressed in terms of incremental cost per quality-adjusted life year (QALY), and costs were be considered from the perspective of the NHS and Personal Social Services. A lifetime horizon was used to capture all costs and benefits associated with leniolisib and relevant comparators		response that the cost-effectiveness analysis presented in the CS adopted a NHS perspective (and not a Personal Social Services perspective).
Subgroups to be considered	None	No subgroups have been considered	N/A In line with NICE final scope	Appropriate
Special considerations including issues related to equity or equality	N/A	N/A	There are currently no licensed treatments available for APDS in the UK. This may lead to sub-optimal and inconsistent use of off-label medicines and variable polypharmacy approaches in the management of APDS.[8] , [9-11]	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			Additionally, individuals of African descent are often faced with inequalities in access to HSCT, due to having the lowest probability of finding an appropriately matched unrelated donor. [12] Access to HSCT may also be restricted for some young people with APDS due to the lack of parental consent. [13]	

Source: CS Table 1 (Section B.1.1) [14]

Abbreviations: APDS = Activated phosphoinositide 3-kinase delta syndrome; CS = company submission; EAG = Evidence Assessment Group; HSCT = Hematopoietic stem cell transplantation; NICE = National Institute of Health and Care Excellence; PSS = personal social services

3.1.1 Population

The eligible population defined in the CS includes adults and adolescents with APDS who are 12 years and older.[14] The anticipated marketing authorisation for leniolisib by the MHRA is expected to provide a dosing recommendation only for patients weighing 45 kg or more. However, the EAG highlights a potential issue with generalisability; the British National Formulary states the mean value weight for 12-year old adolescents is 39kg.[15] In the leniolisib clinical trials, as part of the inclusion criteria, participants were required to weigh over 45 kg. Therefore, the anticipated dosing recommendation for patients weighing 45 kg or more may exclude otherwise eligible adolescents.The company clarified that two ongoing paediatric clinical trials (NCT05438407 and NCT05693129) are evaluating leniolisib at lower doses (20–70 mg bid for patients aged 6–11 years, and 10–50 mg bid for patients aged 1–6 years, respectively).[16,17] These studies will support future applications to extend marketing authorisation for younger individuals with APDS, including recommendations based on body weight.[14]

The company's economic model, described in Section B.3.2.2.2 of the CS was run for a cohort starting treatment at age 15. The company justified this deviation by stating that 15 is the median age of people with APDS in the ESID registry. However, since the population in the NICE scope is 12 and over, the EAG considers this to be a deviation from the final NICE scope. This is also inconsistent with the starting age in a company submitted document.[35] See sections 5.2.1, 5.2.2, 7.1.2 below for more information by the EAG.

3.1.2 Outcomes

The EAG considers the outcomes described in the CS to broadly match the final scope issued by NICE. Additional data was provided for antibiotic use and hearing loss as part of immune deficiency measures and for cytopenias and gastrointestinal manifestations as part of immune dysregulation measures these measures inform the economic model. Lung function measures were provided alongside measures of lung disease (bronchiectasis-associated airway disease and advanced lung disease) these also inform the economic model.

3.1.3 Economic Analysis

The CS described the QoL impacts of APDS (Section B.1.4.2), highlighting how the condition limits the patients' ability to continue with work, education and daily living activities. The company stated that the analysis adopted a National Health Service (NHS) and Personal Social Services perspective (Section B.3) in alignment with the NICE final scope. However, no social care costs (i.e, home support, community services, health visitors etc) appear to be included in the model. The EAG note that the analysis adopted a partial perspective (NHS only), excluding any PSS related costs, and considers this a deviation from the final NICE scope. The company confirmed in their response to points for clarification that only a NHS perspective had been adopted.

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS for the treatment of APDS with leniolisib. Section 4.1 provides a critique of the company's systematic review. Section 4.2 provides a summary of the clinical effectiveness and safety results together with a critique of the included studies. Section 4.3 provides a summary and critique of the indirect treatment comparison, and section 4.4 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) in November 2021, with two updates in May 2023 and April 2024, to identify all clinical evidence on efficacy and safety outcomes associated with leniolisib or other PI3K inhibitors, and current clinical management for the treatment of patients with APDS type 1 and 2. The methods for the company's SLR of clinical evidence are detailed in the CS and Appendix D.[14]

A summary of the EAG's critique is presented in Table 10 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 10: Summary of the EAG's critique of the methods implemented by the company to conduct the systematic literature review

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D1.1, p.9	**Appropriate** An appropriate range of bibliographic databases were used. Additionally, grey literature was searched together with a wide range of conference proceedings and clinical trials registries.
Search strategies	Appendix D1.1, p.9-17	**Some concerns** Search strategies were well reported, although previously indexed subject headings were omitted from all versions of the search and a few abbreviated keywords were found to be missing. As such, it cannot be definitively said that all relevant records were retrieved in the search. There are differences between the original 2021 search and the 2023 update and 2024 targeted search. This may be minor; however, it wasn't explained within the report why the changes were made.
Search filters	N/A	**Not applicable** No search filters were used.
Eligibility criteria	Appendix D1.2	**Some concerns** See section 4.1.2 for further information
Screening	Appendix D1.2	**Some concerns** See section 4.1.3 for further information
Data extraction	Appendix D1.2	**Some concerns** See section 4.1.4 for further information.
Quality appraisal	Appendix D1.2	**Some concerns** See section 4.1.5 for further information.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; SLR = systematic literature review		

4.1.1 Search strategies

Searches were conducted separately for clinical effectiveness (reported in Appendix D.1.1 pg.8), and for economics (cost effectiveness and cost resource use) and health-related quality of life (Appendix G and I respectively). Searches were appraised by the EAG using the Peer Review of Electronic Search Strategies (PRESS) checklist.[18] Critique of the search strategies for cost effectiveness can be found in section 4.1.1. Searches were conducted from the inception date of databases until 11th November 2021, and updated in May 2023 and again in April 2024, so they can be considered up to date.

4.1.1.1 Sources

The EAG reports that a satisfactory search of conference proceedings was performed in American Academy of Allergy, Asthma & Immunology (AAAAI), Clinical Immunology Society (CIS) North American Conference, American Society of Hematology (ASH), International Primary Immunodeficiencies Congress (IPIC), International Congress of Immunology (IUIS) and European Hematology Association (EHA) to supplement the database searches.

4.1.1.2 Subject headings

Appropriate subject headings were used to reflect the current nomenclature, however previously indexed subject headings were omitted from all versions of the search strategy i.e. PHOSPHATIDYLINOSITOL 3-KINASES (2011); Phosphotransferases (1988-1993); Phosphotransferases (Alcohol Group Acceptor) (1994-1997). They were also omitted from the cost-effectiveness and cost resource use searches (critiqued in section 5.1.1).

Without comprehensive testing, it is difficult for the EAG to quantify the effects that all the issues mentioned may have had on search results, but it seems likely the effects would be relatively minor. Overall, the EAG is satisfied that the search for clinical effectiveness studies was conducted appropriately.

4.1.2 Eligibility criteria

The eligibility criteria are said to be pre-defined in a protocol; however, the EAG has not been able to locate a registered protocol for this SLR. The eligibility criteria described in the SLR are generally consistent with the final NICE scope (Table 9) but more broadly defined in terms of population, intervention, outcomes, and study design, aiming for comprehensiveness. The company initially included but later de-prioritised case studies and highlighted seventeen outcome measures included during the SLR updates. Several of these measures are not specifically defined in the final NICE scope but inform the economic model (gastrointestinal manifestations, cytopenias, hearing loss, and bronchiectasis).

The EAG does not consider differences in population and interventions significant because broadening the scope increases the likelihood of identifying all relevant studies. However, the EAG has concerns about the introduction of outcome measures as this increases the likelihood of a type 1 error (i.e. inappropriately concluding that an effect is statistically significant). Additionally, given the small patient population in an orphan condition, data from case studies may have provided additional information about adverse events or other important information relating to pre-specified outcome measures, although we note some case studies inform the findings, as reported in B.2.12 of the CS. Despite this, the EAG have minimal concerns about deprioritising case studies and note that it is common in systematic reviews to exclude study designs that provide less reliable evidence, though this should be specified in advance.

4.1.3 Screening

The screening methods follow recommended practices for the conduct of systematic reviews. For the original SLR, two reviewers independently conducted screening, with a third reviewer arbitrating when disagreements could not be resolved, rapid methods were used for the targeted update conducted on the 9th of April. The PRISMA flow chart for the original SLR and both updates are presented in appendix D of the CS;[19] in summary, 30 unique studies of interventional and observational design were included and underwent synthesis; 88 unique case studies were included, but all did not undergo data extraction or synthesis. Of the 118 included studies (138 records) 10 reported data relating to leniolisib. To avoid erroneously excluding eligible articles during the targeted updatein April 2024, it would have been more reliable for the second reviewer to check the eligibility of all the excluded records at abstract and full-text stages or alternatively to have double-screened a minimum of 20% of the records and ensuring high agreement before continuing to single screening. The EAG considered this issue to be of minimal concern.

4.1.4 Data extraction

Data from 30 interventional or observational studies were extracted by one independent reviewer. A second reviewer assessed missing data and verified the extracted data, and a third reviewer provided conflict resolution when required. The company have not reported if a data extraction form was piloted, and there is no list of pre-specified data items, but it

appears data were extracted into the HST submission tables. The EAG is satisfied with the methods used for data extraction.

The manufacturer reference-linked publications reporting data from the same study to recognise that more than one publication may have contributed to the data entry; it is not clear what steps were taken to avoid double counting. In addition, it is not clear if efforts were made to contact the study authors for missing data. However, this is less of an issue for the trials which form the main basis of the clinical evidence (2201 Part I, II and EI) since the manufacturer, as the trial sponsor, presumably had access to all data.

4.1.5 Quality appraisal

Quality appraisal was conducted by one reviewer with verification by a second. The company used the Downs and Black checklist to appraise the 30 included interventional and observational studies.[19,20] Quality appraisal for the 88 included but deprioritised case studies was not done. No overall risk of bias judgement was provided for each of the individual studies assessed, although as reported in section B.2.12 of the CS, findings from case studies have been used to inform the evidence base and it is unclear how these were selected for inclusion in the narrative synthesis. No attempt has been made to integrate risk of bias findings or to consider the overall impact of study quality on the results.

The company conducted a second assessment of three studies in the company's clinical trial programme (Section B.2.2 CS). A phase 3 randomised-controlled clinical trial (2201 Part II; NCT02435173) was assessed at the study level using the minimum criteria for assessing the risk of bias and generalisability in parallel RCTs, as described in the NICE user guide for company evidence submission template [PMG24].[2] A single-arm, phase 2, open-label, non-randomised clinical trial (2201 Part I; NCT02435173) and an open-label non-randomised extension study (2201 EI; NCT02859727) were assessed using an adapted version of the Critical Appraisal Skills Programme (CASP) Cohort study checklist.[21]

The company considered 2201 Part II to be of high quality and at low risk of bias; judgements to signalling questions and associated rationale are presented alongside the EAG verification in Table 12. The EAG has noted some issues relating to the concealment of allocation and baseline imbalances in prognostic factors.

Non-randomised studies are inherently prone to bias, especially selection bias, due to limitations in the study design. Despite this, single-arm studies are often used for rare conditions with small populations and where there are ethical considerations of withholding potentially effective treatments. The company considered both open-label trials 2201 Part I and 2201 E1 to be of high quality and of low risk of bias, judgements to signalling questions and rationale are presented alongside the EAGs verification in Table 11. The EAG agrees the studies are of high quality but suggests a moderate risk of bias due to inherent limitations of these types of study design and uncertainty around estimates.

The EAG considers the method used to conduct quality assessment reasonable, and both tools used are in line with NICE recommendations. However, assessments undertaken by two reviewers independently are considered the most reliable method to avoid mistakes and the introduction of the reviewer's own biases.

Table 11: Quality assessment verification for Study 2201 Part I and 2201 E1 (reproduced in part from CS table 13)

Study 2201 Part I			Study 2201E1	
CS Critical appraisal		**EAG Critical appraisal**	**CS Critical appraisal**	**EAG Critical appraisal**
Was the cohort recruited in an acceptable way?				
Yes/no/unclear	Yes	Yes	Yes	Yes
Justification	Participant selection was established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria was stored with the source documentation at the study site. As described in Section 4.2.1, the trial population was representative of the wider APDS population.	The investigator ensured that all patients being considered for the study met the eligibility criteria. Patient selection was established by checking through all eligibility criteria at screening. Deviation from any entry criterion excluded a patient from enrolment into the study. The 6 recruited patients met the specified eligibility criteria and were representative of the wider APDS population, though none of the patients were below 16 years of age or weighed less than 52kg.	Participants were enrolled from Study 2201; additionally, participants who were treated previously with PI3Kδ inhibitors other than leniolisib could be enrolled if they met the eligibility criteria at the screening visit. As described in Section B.2.3.2, the trial population was representative of the wider APDS population.	Study 2201E1 provided continuation of leniolisib therapy for those who directly enrolled from Study 2201 (Part I and Part II), including participants who had received placebo in Part II or access to leniolisib therapy for individuals with APDS who previously received treatment with PI3Kδ inhibitors other than leniolisib, such as nemiralisib and seletalisib, if they met the eligibility criteria at screening. Eligibility criteria were highly consistent across Study 2201 and Study 2201E1.
Was the exposure accurately measured to minimise bias?				
Yes/no/unclear	Yes	Yes	Yes	Yes
Justification	All participants received leniolisib. Exposure to leniolisib was reported	All patients received the same dose of leniolisib for the same duration. The starting dose was 10 mg followed by 30 mg and 70 mg bid for 4 weeks at each dose level respectively.	All participants received leniolisib. Exposure to leniolisib was reported	An open label, single arm extension trial, all participants received leniolisib. All participants received the same dose and dosing regimen.

Study 2201 Part I			**Study 2201E1**	
Was the outcome accurately measured to minimise bias?				
Yes/no/unclear	Yes	Yes	Yes	Yes
Justification	Commonly used outcome measures were included. Outcome assessments were performed according to a pre-specified visit schedule for all participants. Outcome measures were objective and were performed according to standardised procedures to minimise bias and variability in assessments. The trial was not blinded, but outcome measures were objective.	Sequential blood samples were collected in all patients up to 8 hours after the first dose administration and after the first dose following each escalation to the next dose level. The same imaging modality was used throughout the study for the same patient. MRI or CT imaging of neck, chest, abdomen and pelvis were performed at screen and again post-treatment. Similar measurement methods were used for all patients.	Commonly used outcome measures were included. Outcome assessments were performed according to a pre-specified visit schedule for all participants. Outcome measures were objective and were performed according to standardised procedures to minimise bias and variability in assessments. The trial was not blinded, but outcome measures were objective.	Safety was assessed as a primary endpoint, safety assessment, method for assessments and recording were specified and followed according to schedule of assessment. The occurrence of AE was sought by indirect questioning of participants during study visits, physical examination findings, laboratory test findings or other assessments. AEs were monitored until they resolved or judged to be permanent.
Have the authors identified all important confounding factors?				
Yes/no/unclear	Yes	Yes	Yes	Yes

Study 2201 Part I			**Study 2201E1**	
Justification	Comprehensive baseline characteristics were measured, including demographic and clinical characteristics and prior concomitant medication.	The baseline characteristics of the participants were clearly stated – all data for background and demographic variables were listed by age group and patient. Summary statistics were provided for patients overall. Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information were listed by age group and patient.	Comprehensive baseline characteristics were measured, including demographic and clinical characteristics and prior concomitant medication.	Baseline demographic characteristics, and prior concomitant medication use were reported for all patients.
Have the authors taken account of the confounding factors in the design and/or analysis?				
Yes/no/unclear	Yes	Yes	Yes	Yes
Justification	Baseline demographic and clinical characteristics are reported in detail, by age group and participant. As confirmed by expert consultants, differences in baseline characteristics are expected to have minimal impact on the results. Due to the small sample size, no subgroup analyses were performed.	The baseline characteristics of the participants were reported. In agreement with the company, the differences in baseline are not expected to have significant impact on the results.	Baseline demographic and clinical characteristics are reported in detail. Subgroup analyses were performed for participants with prior exposure to leniolisib and placebo, as this may have confounded the results.	There were few notable differences in baseline characteristics between extension study patients who had previous exposure to leniolisib and those with previous exposure to placebo. The company performed subgroup analyses for both groups of patients.

Study 2201 Part I			Study 2201E1	
Was the follow-up of participants complete?				
Yes/no/unclear	Yes	Yes	No – study ongoing	No- study ongoing, expected study completion date is January 2027. NCT02859727
Justification	All participants completed the trial	All participants completed the trial. Post-treatment follow-up was completed for all participants. During the four weeks after the last day of dosing, the patients were followed-up for safety. On Day 112 patients underwent the End of Study visit. None of the patients were withdrawn from the study prematurely.	Long-term data from Study 2201E1 (longest expected data collection period of up to six years and three months) is ongoing.	Study is ongoing
How precise (for example, in terms of confidence interval and p values) are the results?				
Yes/no/unclear	Yes, the results are considered precise	Yes	Yes, the results are considered precise.	Yes
Justification	Patient-level results and measures of variability are provided.	Outcome measures and overall safety and efficacy results were provided for all 6 participants. Summary statistics were provided for all parameters of interest. Measures of variability (for example, confidence intervals and p values) were provided.	Measures of variability (e.g. confidence intervals and p values) are provided. Despite the small sample size, Study 2201E1 observed meaningful within-patient results, some of which reached statistical significance.	The study is ongoing, therefore interim analyses were reported. Some results such as for pharmacokinetic parameters were not included in this interim report. Measures of variability such as confidence intervals and p values were only provided for some outcomes.

Abbreviations: APDS: Activated PI3K delta suCRF: case report form; DMC: data monitoring committee; PD: pharmacodynamic; PK: pharmacokinetic.

Source: Rao et al., 2023,[22] Study 2201 Part II CSR, [23]

Table 12: Quality assessment verification for Study 2201 Part II (reproduced in part from CS table 13)

Study 2201 Part II			
CS Critical appraisal		**EAG Critical appraisal**	
Was randomisation carried out appropriately?			
Yes/no/unclear	Yes	Yes/no/unclear	Yes
Justification	Randomisation numbers were assigned in an ascending, sequential order to eligible participants. The investigator entered the randomisation number on the case report form (CRF). A randomisation list was produced using a validated system that automated the randomisation assignment of treatment arms to randomisation numbers in the specified ratio. This procedure ensured that treatment assignment was unbiased.	Justification	A validated automated system generated the random allocation sequence and assigned eligible participants to treatment and control arms in ascending, sequential order. Novartis Drug Supply Management oversaw the process.[24]
Was the concealment of treatment allocation adequate?			
Yes/no/unclear	Yes	Yes/no/unclear	Unclear

Study 2201 Part II			
Justification	Randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone involved in the study, with the following exceptions: data monitoring committee (DMC) members, unblinded pharmacist or authorised designee at the site, unblinded monitor (where used) and the PK bioanalyst. This procedure ensured that treatment allocation was concealed.	Justification	The EAG were unable to identify information to confirm the random sequence allocation was adequately concealed before and until participants were assigned. Specifically, we were unable to locate information regarding the mechanism used for concealment. The EAG identified the following information in the protocol: *"randomisation numbers will be assigned in ascending sequential order"* and *"randomization numbers for part II of the study will be assigned in ascending, sequential order to eligible subjects (see Site Operations Manual for details). The investigator will enter the randomization/treatment number on the CRF"* In addition, the randomisation process had oversight from the Novartis Drug Supply Management chain and "*the randomisation scheme for subjects was planned to be reviewed and approved by a member of the Novartis IIS randomisation Group*".[24] This indicates the process was not done by an external organisation, independent of the enrolment personnel.
Were the groups similar at outset of the study in terms of prognostic factors?			
Yes/no/unclear	Yes	Yes/no/unclear	No

Study 2201 Part II			
Justification	Baseline demographic and clinical characteristics were generally well balanced between the leniolisib and placebo groups. As is common in ultra-rare diseases where trials have small sample sizes, some differences in baseline clinical characteristics between the treatment groups were identified (specifically for history of bronchiectasis and gastrointestinal manifestations) and have been discussed further in Section B2.2.2.	Justification	Clinical characteristics show differences in some prognostic factors between comparator and treatment arms. Specifically, there are substantial differences in bronchiectasis and gastrointestinal disease. In addition, there are smaller differences in multiple other factors in the placebo arm, including history of pneumonia, asthma, herpes simplex, and overall neoplasms benign, malignant and unspecified. All these factors are more prevalent in the placebo group.[14,22] It is difficult to say if the imbalances are indicative of systematic error or have occurred by chance, although we agree with the company that imbalance occurring by chance in very small heterogenous populations is very likely. Nonetheless, the imbalance exists, and because there are substantial imbalances in more than one factor we have judged this question to be 'no'. Potential implications of the imbalances are discussed outside of issues related to the risk of bias in section 4.2.2.2.
Were the care providers, participants and outcome assessors blind to treatment allocation?			
Yes/no/unclear	Yes	Yes/no/unclear	Yes
Justification	Study 2201 Part II was a triple-blinded study: the participants, investigator staff, sponsor persons performing the assessments and data analysts remained blinded to the identity of study treatments. Study drugs were identical in packaging, labelling, schedule of administration, appearance and odour.	Justification	Participants, investigator staff, and sponsor personnel performing the assessments and data analysis were blinded to the identity of participants on study treatment. Study drugs were identical in appearance, odour, packaging, labelling, and schedule. Therefore, bias due to deviations from intended interventions and bias in the measurement of the outcome because of non-blinding is unlikely.
Were there any unexpected imbalances in dropouts between groups?			
Yes/no/unclear	No	Yes/no/unclear	No

Study 2201 Part II			
Justification	No participants withdrew or discontinued treatment prematurely in Study 2201 Part II.	Justification	A participant flow diagram is reported by Rao 2023 and describes participants who were randomly assigned, received intended treatment, and analysed.[22] No participants appear to have discontinued or withdrawn from 2201 Part II, indicating good acceptability and tolerability.
Is there any evidence to suggest that the authors measured more outcomes than they reported?			
Yes/no/unclear	No	Yes/no/unclear	No
Justification	There was no evidence to suggest the authors measured more outcomes than they reported. Conclusions from investigator narratives are drawn, and clearly labelled. Post hoc analyses were conducted on data collected as part of the pre-specified outcomes, and were clearly labelled.	Justification	The company have provided data for a wide range of endpoints and outcomes, some endpoints relate to broadly defined outcome domains/manifestations. Many endpoints have been analyzed in different ways to provide supporting information where primary analysis is limited and to aid the interpretation of clinically meaningful differences, but all are transparently reported. Additionally, the company have provided additional data relating to hepatomegaly upon request. The EAG noted the inclusion of a key primary endpoint (change in naïve B cells out of total B cells) in version 7 of the protocol (July 2017) but considered this of limited concern because it was before the study commenced and before any data collection had taken place (December 2017). The company have clearly reported post-hoc analyses, relating mostly to the identification of clinically meaningful differences.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?			
Yes/no/unclear	No	Yes/no/unclear	No

Justification	All 31 participants who were randomised to treatment were included in the safety analysis set. For the efficacy analyses, an intention-to-treat analysis was not conducted. The PD analysis set consisted of all participants with any available PD data who received any study drug and experienced no protocol deviations with relevant impact on PD data. However, this is unlikely to have introduced bias into the study results: The first principle of the intention-to-treat analysis is to analyse participants in the intervention groups to which they were randomised, regardless of the interventions they actually received. In Study 2201 Part II, all participants received the intervention to which they were randomised, so this principle is fulfilled by the PD analysis set, and there should be no risk of bias with respect to deviations from intended interventions. As described in Section B2.3.1, four participants were excluded from the PD analysis set due to protocol deviations. Three of these were reported as deviations from inclusion criteria, i.e. participants were actually ineligible for inclusion in the trial, rather than representing post-randomisation exclusions of eligible participants. Therefore, these exclusions should not introduce bias into the results. The deviations from inclusion criteria occurred in line with the 2:1 treatment	Justification	The intervention effect of interest was adherence to the intervention. Four people were excluded from the analysis and reasons provided in the published report by Rao 2023.[22]

Study 2201 Part II			
	allocation ratio (leniolisib: n=2; placebo: n=1), so the benefit of randomisation is likely to have been maintained despite these exclusions. Only one participant excluded from the PD analysis set was eligible for the trial. Therefore, overall, the impact of not conducting an intention-to-treat analysis is expected to be insignificant. Supportive analyses including participants with protocol deviations support results of the main analyses.		

Abbreviations: CRF: case report form; DMC: data monitoring committee; PD: pharmacodynamic; PK: pharmacokinetic.

Source: Rao et al., 2023,[22] Study 2201 Part II CSR, [23]

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The CS includes three clinical studies that examine the efficacy and safety of leniolisib for the treatment of APDS: 2201 Part I, a phase 2 open-label dose-finding study; 2201 Part II, a pivotal RCT; and 2201EI, an open-label extension of Study 2201 Part I and Part II. A total of 38 people received leniolisib across the clinical trial programme.

A summary of trial methodology for the leniolisib clinical trial programme, including sample size, study duration and endpoints, is provided in Table 13.

Table 13: Summary of trial methodology of the leniolisb clinical trials (adapted from Table 6 and section B.2.3.1 of the CS)[14]

	Study 2201 Part I (N=6) (NCT02435173)	**Study 2201 Part II (N=31) (NCT02435173)**	**Study 2201E1 (N=37) (NCT02859727)**
Study design	Phase II, international, multicentre, open-label, non-randomised, within-participant, dose-finding, dose escalation study	Phase III, triple-blinded, randomised, international, multicentre, placebo-controlled study	Open-label, non-randomised, international, multicentre extension study
Study locations	Study 2201 Part I and Part II were conducted at ten sites in nine countries: Belarus, the Czech Republic, Germany, Ireland, Italy, the Netherlands, the Russian Federation, the United Kingdom and the USA		Study 2201E1 was conducted at eight sites in seven countries: Belarus, the Czech Republic, Germany, Italy, the Netherlands, the Russian Federation and the USA
Study duration	12 weeks		Six years and three months
Eligibility criteria	See Table 96 in Appendix N.1.3 for a full list of the eligibility criteria.[19] Participants aged 12-75 years with a APDS-associated pathogenic gene variant in *PI3KCD* or *PIK3R1.* They must exhibit nodal and/or extra nodal lymphoproliferation and at least one measurable nodal lesion on CT/MRI and have a clinical history compatible with APDS. Exclusion criteria include surgical or medical conditions, including HSCT that could affect the pharmacokinetics of leniolisib.	See Table 97 in Appendix N.1.3 for a full list of the eligibility criteria.[19] Participants aged 12-75 years with a APDS-associated pathogenic gene variant in *PI3KCD* or *PIK3R1*. They must exhibit nodal and/or extra nodal lymphoproliferation and at least one measurable nodal lesion on CT/MRI and have a clinical history compatible with APDS. Exclusion criteria include surgical or medical conditions, including HSCT, that could affect the pharmacokinetics of leniolisib.	See Table 98 in Appendix N.1.3 for a full list of the eligibility criteria.[19] Participants aged 12-75 years with a APDS-associated pathogenic gene variant in *PI3KCD* or *PIK3R1*. Exclusion criteria include surgical or medical conditions, including HSCT, that may alter the pharmacokinetics of leniolisib.
Interventions	Three increasing doses of leniolisib (10 mg, 30 mg, 70 mg bid)	2:1 ratio of leniolisib 70 mg or placebo bid	Leniolisib 70 mg bid

Co-primary endpoints	Safety parameters including AEs, physical exam, vital signs, ECG, safety laboratory (haematology, blood chemistry, urinalysis) Dose-PD and PK/PD relationship of leniolisib via single and multiple dose concentrations of leniolisib, and pAkt inhibition in unstimulated and stimulated whole blood	Immunophenotype: CfB in % naïve B cells out of total B cells Lymphadenopathy: CfB in the log10 transformed SPD in up to six of the largest lesions from measurable nodal/lymph node index lesions, selected as per the Cheson methodology from MRI or CT imaging	Safety parameters including AEs, physical exam, vital signs, ECG, safety laboratory (haematology, blood chemistry, urinalysis)
Key secondary endpoints	SF-36, PtGA scores and individual participant narratives	3D volume of index and measurable non-index lesions selected as per the Cheson methodology, and 3D volume and bi-dimensional sizes of spleen SF-36, PtGA scores and individual participant narratives Safety parameters including AEs, physical exam, vital signs, ECG, safety laboratory (haematology, blood chemistry, urinalysis)	Frequencies of infections and other disease complications SF-36, PtGA scores and individual participant narratives
Pre-planned subgroups	N/A	Age group: <18 years and ≥18 years Sex: male and female (added to SAP prior to database lock) Genetic diagnosis: APDS1 and APDS2 (added to SAP post database lock)	N/A

Source: CS (section B.2.3.1)[14]

Abbreviations: 3D = three-dimensional; AE = adverse events; APDS = activated PI3K delta syndrome; bid = Bis In Die (twice daily); bpm = beats per minute; CfB = change from baseline; CT = computed tomography; CYP1A2 = cytochrome P450 1A2; CYP3A = cytochrome P4503A; ECG = electrocardiogram; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; mTOR = mammalian target of rapamycin; pAkt - phosphorylated protein kinase B; PD = pharmacodynamic; PI3Kδ = phosphoinositide 3-kinase delta; PI3KCD = phosphoinositide 3-kinase catalytic subunit delta; PI3KR1: phosphoinositide 3-kinase regulatory subunit alpha; PK = pharmacokinetic; PtGA = patient global assessment; SAP = statistical analysis plan; SD = standard deviation; SF-36 = 36-item short form survey; SPD = sum of product of diameters; USA = United States of America; WPAI-CIQ = work productivity and activity impairment plus classroom impairment questionnaire

4.2.1 Study 2201 Part I

A summary of the EAG's critique of the design, conduct and analysis of Study 2201 Part I is presented in Table 14.

Table 14: Summary of EAG's critique on the design, conduct and analysis of Study 2201 Part I trial

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Treatment	B.2.2, Table 6	**Appropriate** The trial comprised a dose escalation phase using three increasing doses of leniolisib (10 mg, 30 mg, 70 mg bid) for a study duration of 12 weeks. All patients received the same dose of leniolisib for the same duration.
Randomisation	NA	Not applicable
Allocation concealment	NA	Not applicable
Eligibility criteria	B.2.2, Table 5	**Appropriate** Eligible participants were adolescents and adults aged 12 to 75 years with a minimum weight of 45kg (for age 12-15) or BMI of 18-35 kg/m^2 (for age 16+) with documented APDS/PASLI (n=6). The EAG agrees that this was in line with the NICE decision problem.
Blinding	NA	Not applicable
Baseline characteristics	Interim Clinical Study Report (Part I) p.46 - 47	**Some concerns** The baseline characteristics of the participants were clearly stated – all data for background and demographic variables were listed by age group and patient. Baseline demographic characteristics were representative of the wider APDS population. However, the youngest participant enrolled was 16 years old and the weight range for the 6 participants was 52.9 – 73.2kg. The EAG have concerns that none of the enrolled participants had the minimum weight of 45kg and age 12 years old.
Dropout rate	B.2.5 Table 14	**Appropriate** No participants withdrew or discontinued treatment prematurely. All participants completed the trial.
Statistical analyses	Interim Clinical Study Report (Part I)	**Appropriate** The primary parameter used as PD marker to select the dose for Part II was % pAkt positive B cells (unstimulated and stimulated samples). A concentration-response model was fitted to link systemic drug concentration and pAkt inhibition at each measured time point. The EAG agrees that this is an appropriate approach.

Outcome measures	Interim Clinical Study Report (Part I) p. 48, 74-75	**Appropriate** Safety, pharmacokinetic and pharmacodynamic parameters were determined in all patients treated with leniolisib. Lymph node sizes, transitional and naïve B cell frequencies (as a proportion out of total B cells) were observed and reported. Effect of leniolisib on PI3Kδ pathway, as assessed by a dose and concentration dependent inhibition of pAkt, was reported.
Results: Efficacy outcomes	Interim Clinical Study Report (Part I) p.54-55, 66-67, 64-65	**Some concerns** PI3Kδ pathway, as assessed by phospho-Akt-positive B cells, was suppressed in a dose and concentration dependent manner over the dose range explored. Lymph node sizes (i.e., sum of products of diameters of pre-identified index lymph nodes) were reduced by 40% and spleen volumes were reduced by 39%. As a proportion of total B cells, a reduction in the frequency of elevated transitional B cells (from 38% to 10%) and an increase of naïve B cell frequency (from 32% to 78%) was observed. There was no appreciable change in liver volume. Assessment of the efficacy of leniolisib to modify health-related quality of life in patients with APDS/PASLI through SF-36 (Short Form 36) Survey and WPAI-CIQ were reported as not conclusive. There were elevations in clinical chemistry parameters of systemic inflammation in APDS/PASLI: High-sensitivity C-reactive protein (hsCRP)/Lactate dehydrogenase (LDH). See section 4.2.1.1 for further discussion of efficacy outcomes.
Results: Adverse events	B.2.10 p112-119; Interim Clinical Study Report (Part I) 12.2 p76-87	**Appropriate** The median duration of leniolisib exposure (11.93 weeks) was in line with the 12 week-duration of the study. There were no deaths or discontinuations reported in Part I of the study. There were no serious adverse events (SAEs) reported during Part I of the study. There were no other significant adverse events reported. No study-drug related AEs were reported. The extension trial reported that leniolisib remained well tolerated throughout a median exposure of 154.71 weeks.[25]
Results: Subgroup analyses		**Not applicable** No subgroup analysis was undertaken

Abbreviations: Akt = Protein kinase B; AUC = area under the plasma concentration-time curve; Cmax = observed maximum plasma concentration following drug administration [mass/volume]; CS = company submission; Ctrough = observed plasma concentration at 12 hours post last dose [mass/volume]; EAG = Evidence Assessment Group; APDS/PASLI = Activated PI3K delta syndrome/ p110δ-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency; bid = Bis In Die (twice daily); NICE = National Institute for Health and Care Excellence; pAkt = Phosphorylated Akt; SF-36 = Short Form 36; WPAI-CIQ = Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire; hsCRP/LDH = High-sensitivity C-reactive protein Lactate dehydrogenase; SAEs = serious adverse events; AE = adverse events.

4.2.1.1 Results: Efficacy outcomes

Lymphoproliferation can lead to enlargement of the spleen (splenomegaly) and/or liver (hepatomegaly). For the assessment of the impact of leniolisib on lymphoproliferation, liver and spleen 3D volumes were measured. The company reported that treatment with leniolisib led to no appreciable change in liver volume. In response to the clarification of questions, the company provided a justification for this as "in APDS, it is less common for lymphoproliferation to occur in the liver; lymphoproliferative changes are most commonly seen in the lymph nodes and spleen" (Question A5 PfC p.5).[26] Additionally, the company reported that supplementary analyses of Study 2201 Part II demonstrated a statistically significant reduction with leniolisib compared with placebo in liver bi-dimensional size (p=0.0361) (Question A5 PfC p.6).[26]

In the assessment of the efficacy of leniolisib to modify health-related quality of life in patients with APDS/PASLI through SF-36 (Short Form 36) Survey and Work Productivity and Activity Impairment (WPAI) plus Classroom Impairment (CIQ) Questionnaire (WPAI-CIQ), it was reported that both assessments did not provide conclusive outcomes and that these results may be due to the relatively small sample size, the relatively short evaluation period and the heterogeneity of the patient group including adolescent and adult patients (age range: 16 – 31 years). However, both SF-36 and WPAI-CIQ assessments did not show statistically significant results in the Part II of the study which enrolled a larger sample size.

As part of secondary objectives, measurements were conducted to assess the efficacy of leniolisib in reducing clinical chemistry parameters of systemic inflammation in APDS/PASLI: High-sensitivity C-reactive protein (hsCRP)/Lactate dehydrogenase (LDH). However, of the six patients enrolled in Part I:

- three demonstrated 'isolated' elevations of hsCRP values (9.8 mg/L on Day 84; increase from 6.5 mg/L (on day 35) to 19.8 mg/L on Day EoS; 14.2mg/L on screening). The normal hsCRP range is 0-5 mg/L.
- one patient had a single instance of high LDH value (284 U/L) during the study (on Day 71). The normal LDH range is 100-242 U/L.

4.2.2 Study 2201 Part II

Evidence for the effectiveness of leniolisib in patients with APDS is partly informed by the pivotal phase III study; 2201 Part II (NCT02435173).[4] This randomised controlled trial (RCT) design was robust, using an appropriate randomisation method; patients, investigators and the sponsor were appropriately blinded. However, due to challenges inherent to rare disease populations, the sample size is small (n=31), and the benefits of randomisation are more apparent in much larger samples. Given the condition was characterised in 2013 and the number of people with APDS in England is estimated to be [redacted], the EAG agrees that the number of patients enrolled in the trial is appropriate relative to the overall population.[14] The participants are a separate cohort from those enrolled in the earlier dose-finding 2201 Part 1.

Study 2201 Part II compared the effectiveness of leniolisib against placebo plus selected symptomatic treatments over a 12-week period between December 2017 and August 2021.[23] It was a multi-centre, international trial with 31 patients enrolled across nine countries (United States of America, Belarus, Czechia, Germany, Ireland, Italy, the Netherlands, Russia and Belfast in the UK). Whilst there was one trial site in the UK, the EAG note a limited number of participants from the UK and none from England, which could limit the generalisability of findings to the UK setting. The company provided clarification and evidence to support the study's generalisability (Question A11 PfC).[26] Specifically, clinician confirmation to confirm that the baseline characteristics observed in the study do align with those seen in routine clinical practice and further evidence from the European Society for Immunodeficiencies (ESID) registry and the Early Access Programme (EAP). Despite some variability in clinical characteristics observed in the trial compared to the registry, which could be due to the small sample size the EAG is satisfied with the company's clarification and concur the trial results are likely generalisable to APDS patients seen in England (Question A11 PfC).[26]

A summary of the EAG's critique of the design, conduct and analysis of Study 2201 Part II is presented in Table 15.

Table 15: Summary of EAG's critique of the design, conduct and analysis of Study 2201 Part II

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Eligibility criteria	Appendix N.1.3, Table 97	**Key issue** The eligibility criteria are described briefly in Table 13 above and more comprehensively in Appendix N.1.3 of the CS. The eligibility criteria for the treatment group aligns with the population described in the final NICE scope. However, the EAG does not consider the comparator arm to be representative of UK established clinical management as defined in the NICE decision problem. See section 4.2.2.1 for further information.
Treatment	B.2.3.1, Table 6	**Appropriate** The EAG is satisfied that the intervention is appropriate; a fixed dose of 70 mg of leniolisib was delivered twice daily over a 12-week period.
Randomisation	B.2.3.1, Table 6	**Appropriate** The random sequence was generated using a validated system that automated the random numbers for assignment to treatment arms in the specified ratio (leniolisib (n=21) or placebo (n=10)). The 2:1 ratio was specified in v07 of the protocol (July 2017) before the study commenced. The EAG is satisfied that randomisation was appropriately conducted.[24]
Concealment of treatment allocation	B.2.5, table 13	**Some concerns** The exact procedure used to preserve random allocation was insufficiently described. Version 2 of the protocol states, "*randomization numbers for part II of*

		the study will be assigned in ascending, sequential order to eligible subjects (see Site Operations Manual for details). The investigator will enter the randomization/treatment number on the CRF"[24] See the EAG response to the company's critical appraisal in Table 12, section 4.1.5.
Blinding	B.2.3.1	**Appropriate** This was a triple-blinded study. The participant, investigator, and sponsors were masked to treatment assignment throughout the study, minimising the potential for performance and detection bias.
Baseline characteristics	B.2.3.2, Table 9	**Some concerns** There are some imbalances in baseline clinical characteristics (section 4.2.2.2 below).
Dropout rate	B.2.5, Table 13	**Appropriate** No participants withdrew or discontinued treatment prematurely.
Statistical analyses	B.2.4.2	**Some concerns** Sample size calculations were informed by standard deviations observed in 2201 Part 1 (SD=0.14) for lymphadenopathy. Using a two-sided alpha level of 0.05 a sample size of 30 participants (leniolisib n=20; placebo n=10) was estimated to provide 97% power to detect statistically significant differences. A sample size of 30 was estimated to provide sufficient power (at least 78%) to achieve statistically significant p-values in both co-primary endpoints. Three data sets were analysed: Pharmacokinetic (PK), pharmacodynamic (PD) and safety. The PD data set (All participants with any PD data who received any study drug and no protocol deviations) was used for the analysis of covariance for each co-primary endpoint. A subset of the PD data (B-PD) was used to analyse positive change from baseline (CfB) in percentage of naïve B cells out of total B cells and included only patients with <48% naïve B cells at baseline (n=13). The B-PD data analyses a reduced sample and is therefore underpowered, leading to uncertainties in the magnitude of the effect. However, supportive analysis using the full PD data set is provided and demonstrates a similar trend. For lymphadenopathy, patients with zero nodes at baseline were excluded from the primary analysis. To address the possibility of multiplicity both co-primary endpoints needed to be statistically significant to draw inferences.
Outcome measures	B.2.2, Table 5 Clarification questions. 7-9	**Some concerns** The company provided data for 19 endpoints and outcomes related to the following broad categories: immunophenotype, immune dysregulation, immune deficiency, lung disease, fatigue, malignancy and mortality, HRQoL and adverse events.

		The EAG has some concerns regarding the clinical validity of the co-primary outcome measures (section 4.2.2.4.1).
Results: Efficacy outcomes	B.2.6	**Some concerns** Both co-primary endpoints met statistical significance. See section 4.2.2.4.1 for further details
Results: Adverse events	B.2.10; Clinical Study Report	**Appropriate** The incidence of patients reporting study-drug related AEs was comparable between the two treatment groups. Of those receiving leniolisib, 23.8% (5/21) reported study-drug-related AEs compared to 30% (3/10) in placebo. The majority of patients (74.2%) reported Grade 1 AEs. Eight out of 31 patients had Grade 3 or Grade 4 AEs. All 8 patients who reported study-drug related AEs belonged to genetic diagnosis APDS1; this might be explained by the higher known prevalence of APDS1 and subsequent numbers enrolled in the trial compared to APDS2. All SAEs reported throughout Study 2201 Part II were assessed by the investigator as being unrelated to study treatment. There were no discontinuations in Part II. However, [redacted] pulmonary hypertension approximately 3.5 months after the final dose of study medication; [redacted] was reported as unrelated to the study treatment.
Results: Subgroup analyses	B.2.7; Appendix E	**Appropriate** In relation to the co-primary endpoints an *A priori* planned subgroup analysis was undertaken to assess the impact of age (<18 years and ≥18 years). Post-hoc subgroup analysis to assess difference in sex (male vs female) and genetic diagnosis (APDS1 vs APDS2) was also reported. The results are generally consistent among the overall population. However, it is important to note that findings are exploratory; sample sizes are very small with wide confidence intervals, especially for adolescents in the age assessment (see Appendix E.1.2. Tables 26 – 27).

Abbreviations: AE = adverse event; APDS = Activated PI3K Delta Syndrome; bid = Bis In Die (twice daily); CS = company submission; CfB = change from baseline; EAG = Evidence Assessment Group; HRQoL = health related quality of life; IgM = immunoglobulin; mTOR = mammalian target of rapamycin; PD = pharmacodynamics; PGA = Physician's Global Assessment; PK =Pharmacokinetics; PtGA = Patient's Global Assessment; SF-36 = 36-Item Short Form Survey; SAE = serious adverse event; SD = standard deviation; WPAI-CIQ= Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire

4.2.2.1 Eligibility criteria – comparator arm

Participants in the comparator arm received placebo plus a restricted selection of symptomatic treatments.

Sections B.2.3.1 and B.1.4.3 of the CS, along with expert clinical advice to the EAG, confirm that immunosuppressive medication, specifically mTOR inhibitors, steroids and rituximab, typically form established clinical management for APDS in the UK.

Previous use of certain immunosuppressive medications was prohibited in the clinical trial programme if they were administered within a certain timeframe prior to the first dosing of leniolisib or placebo. To be eligible for enrolment participants who had previously used certain immunosuppressive medications were required to complete a protocol defined washout period (see Table 16 for prohibited medications and corresponding washout criteria). More importantly, concurrent use of some classes of immunosuppressive medications, including mTOR inhibitors (sirolimus, everolimus) and rituximab, which form current clinical management, was prohibited in both the treatment and control arms of Study 2201 Part II. Table 16 provides a non-exhaustive list of immunosuppressive treatments that were prohibited throughout Study 2201 Part II, along with corresponding washout criteria.

The company prohibited the use of immunosuppressives due to evidence suggesting they can lead to an increased risk of infections.[24,27] Four out of five clinicians who participated in expert elicitation indicated they would not combine sirolimus, rituximab, mycophenolate mofetil or cyclosporin with a PI3K inhibitor. Therefore there is justification for their exclusion in a treatment arm, but the EAG considered the exclusion of these treatments for the placebo group to be a substantial limitation. Clinical advisors to the EAG pointed out that APDS patients receiving standard care in the UK may receive these medications. Therefore, the placebo group's treatment regimen was considered to be less intensive than that expected in current clinical practice.

In order to overcome this issue, the company carried out an indirect treatment comparison of leniolisib versus an external control group taken from the ESID Registry who were receiving established clinical care, including immunosuppressive therapies and HSCT (see the EAG critique in section 4.3).

Table 16: Prohibited immunosuppressive co-medications across the clinical trial programmes (2201 Part I, II and EI), reproduced from section B.2.3.1 of the CS

Examples of prohibited immunosuppressive co-medications[a]	Time frame within which co-medication was not permitted
Belimumab Cyclophosphamide	Not permitted within six months prior to first dosing of the study medication
B cell depleting medication (e.g., rituximab)	Not permitted within six months prior to first dosing of the study medication If previously received, absolute B lymphocyte counts in the blood must have regained normal values
Cyclosporine A Mycophenolate 6-mercaptopurine Azathioprine Methotrexate	Not permitted within three months prior to first dosing of the study medication
mTOR inhibitors (e.g. sirolimus, everolimus) Non-selective PI3K inhibitors Selective PI3Kδ inhibitors	Not permitted within six weeks prior to first dosing of the study medication Short-term use for up to a total of five days was allowed but only up to one month prior to enrolment in the study
Glucocorticoids above 10 or 25 mg prednisone or equivalent per day (Study 2201 Part I and Study 2201 Part II/Study 2201E1, respectively)	Not permitted within two weeks prior to first dosing of the study medication

Source: CS Section B.2.3.1
Footnotes: [a]Other immunosuppressive medications where the effects were expected to persist at start of dosing of the study medication were also prohibited.
Abbreviations: mTOR: mammalian target of rapamycin; PI3K: phosphoinositide-3 kinase.

4.2.2.2 Baseline characteristics

Baseline demographics and medication use presented in Table 8 and 10 of the CS are generally comparable across the leniolisib and placebo arms, except from previous sirolimus treatment which was more common in the placebo group (30.0%) compared to the leniolisib group (19.0%).[14]

As noted by the company, there are substantial imbalances in some baseline clinical characteristics (Table 9 of the CS), namely, bronchiectasis and gastrointestinal disorder which are more prevalent in patients randomized to the control arm. Additionally, there are smaller differences in multiple other factors in the placebo arm, including history of pneumonia, asthma, herpes simplex, and overall neoplasms benign, malignant and unspecified. The company suggests imbalances may be due to reporting issues across sites and the limited sample size. While the EAG agrees that balancing baseline characteristics in heterogeneous, ultra-rare populations is difficult, the data nonetheless demonstrates that the participants randomised to the control arm were more severely impacted at baseline compared to participants randomised to the treatment arm, potentially bringing uncertainty into the observed treatment effect for leniolisib. The EAG also note a potential cumulative impact of this, and the issues noted above in section 4.2.2.1 regarding the comparator arm which is less intensive than UK standard of care.

4.2.2.3 Outcome measures

The following measures informed the economic model: lymphadenopathy, splenomegaly, cytopenias, bronchiectasis-associated airway disease, advanced lung disease, malignancy and mortality, infection rates, rate of IRT use and rate of antibiotic use. One endpoint used to inform the economic model, antibiotic use, does not appear to be specified explicitly in the final NICE scope.

The co-primary endpoints used to assess the effect of leniolisib did not inform the economic model. Improvement in immunophenotype was measured using B cell normalisation (positive CfB in percentage of naïve B cells out of total B cells using flow cytometry) and improvement in lymphoproliferation was measured by reduction in lymphadenopathy/ reductions in index lesion size (CfB in the log10 transformed SPD in up to six of the largest lesions from measurable nodal/lymph node index lesions, selected as per the Cheson methodology from MRI or CT imaging).

4.2.2.4 Key Results

4.2.2.4.1 Co-primary endpoints

Both co-primary surrogate endpoints used to measure immunophenotype normalisation and reduction in lymphoproliferation were statistically significant.

For improvement in immunophenotype, the adjusted mean change in naïve B cells as a percentage of total B cells from baseline to Day 85 between leniolisib (n=8) and placebo (n=5) was 37.30% (95% CI: 24.06, 50.54; *P*=.0002). The B-PD data set included patients with <48% naïve B cells at baseline (n=13), thereby reducing the sample size. Supportive analyses using the full PD data set (n=21) are presented in Table 17 below. A modified Delphi with treating clinicians (n=24) determined a ≥20% increase in the percentage of naïve B cells of total B cells after 12 weeks of treatment would be clinically meaningful. In a post hoc analysis of the B-PD analysis set, all patients (n=12) in the leniolisib arm achieved a ≥20% increase compared to none (n=5) in placebo, further information regarding responder analysis is presented in Section B.2.6.1, Table 17 of the CS.[14] The company reports observing increases in the percentage of naïve B cells at each time point throughout OLE up to day 252 (~8 months), see section B.2.6.1 of the CS.

For reduction in lymphadenopathy (i.e., reduction in index lesion size), the log10 transformed SPD of index lesions showed a difference in adjusted mean difference of -0.25, (95% CI: -0.38, -0.12; n=26; *P* = .0006) at week 12. Supportive analysis, which includes all patients from the PD analysis set regardless of the number of lesions at baseline, is provided in Table 17 below. A modified Delphi study with treating clinicians (n=24) described a change of ≥20% (adults) or ≥25% (adolescents) from baseline index lesion SPD as a clinically meaningful change following three months of treatment. Post hoc analysis reported a risk difference of 0.64 (95% CI: 0.16, 0.89; n=27) see Section B2.6.2, Table 19 of the CS for further information relating to responder analysis relating to 2201 Part II.[14] The company reports that after 24-36 weeks of treatment with leniolisib (2201 E1) 24 out of 30 participants (80%) achieved the responder threshold. For adults, this is identified as a reduction from baseline in the index SPD by at least 30% for adults and 45% for adolescents at six months, see section B.2.6.2, Table 20 of the CS for further information regarding responder analysis.

The EAG considers there to be uncertainty about the validity of the surrogate endpoints used, particularly the novel measure of naïve B-cells to total B-cells, in reliably predicting long-term clinical benefits. The company's correlation analysis in 2024 examined the link between surrogate biomarkers and patient outcomes, noting a level 2 evidence association between changes in naïve B-cells and long-term infection rates, as defined by EUnetHTA. Additionally, a 2023 modified Delphi survey retrospectively identified relevant variables and clinically meaningful differences for naïve B cells and lymphadenopathy. Despite some biological plausibility and evidence supporting naïve B cells as an endpoint, evidence of a

consistent association remains unclear. For further details, refer to the company's clarification on lymphadenopathy and immunophenotype (B cell normalisation) (Question A7).[26]

Table 17 Clinical effectiveness data for the co-primary endpoints used in 2201 Part II at Day 85 (Reproduced from Table 16 and 18 of the CS) [14]

	Adjusted mean CfB (SE)[c] for naive B cells Mean change (SE) for index lesions	Comparison of adjusted means			
		Difference	SE	95% CI	2-sided p-value
CfB of percentage of naïve B cell to total B-cells					
Primary efficacy analysis (B-PD analysis set)[a]					
Leniolisib 70 mg bid (n=8)	37.39 (5.35)	37.30	5.74	24.06, 50.54	0.0002
Placebo (n=5)	0.09 (6.66)				
Supportive analysis (PD analysis set)[b]					
Leniolisib 70 mg bid (n=13)	34.70 (5.66)	27.94	6.09	15.02, 40.85	0.0003
Placebo (n=8)	6.76 (5.67)				
CfB in log10 transformed SPD of index lesions					
Primary efficacy analysis (PD analysis set: log10 transformed SPD)[d]					
Leniolisib 70 mg bid (n=18)	−0.27 (0.04)	−0.25	0.06	−0.38, −0.12	0.0006
Placebo (n=8)	−0.02 (0.06)				
Supportive analysis (PD analysis set: sum of square root of the product of diameters)[e]					
Leniolisib 70 mg bid (n=19)	−23.68 (4.17)	−21.91	6.86	−36.12, −7.69	0.0042
Placebo (n=8)	−1.78 (6.11)				

Footnotes: [a]Only included participants in the PD analysis set with fewer than 48% naïve B cells out of total B cells at baseline. [b]Included all participants in the PD analysis set apart from six participants, for the following reasons: one participant did not have a baseline measurement of total B cells; one had no naïve B cells at baseline and did not have post-baseline naïve B cell assessments; and four had naïve B cell percentages of less than 48% at baseline but no assessment was performed at Day 85. [c]Data were analysed using an ANCOVA model with treatment as a fixed effect and baseline characteristics as a covariate. The use of glucocorticoids and concomitant immune replacement therapy at baseline were both included as categorical (Yes/No) covariates. Baseline was defined as the arithmetic mean of the baseline and Day 1 values when both were available, and if either baseline or the Day 1 value were missing, the existing value was used.[d]One participant receiving leniolisib was excluded from the PD analysis set because the baseline index node fully resolved by Day 85, and therefore the "log10 transformed SPD of index lesions" could not be derived. [e]Included all participants from the PD analysis set regardless of the number of lesions at baseline.
Abbreviations: bid: Bis In Die (twice daily); CfB: change from baseline; CI: confidence interval; PD: pharmacodynamics; SE: standard error: SPD: sum of product diameters.
Source: Table 16 and 18 of the CS. [14]

4.2.2.4.2 IgM and Infection

Immunoglobulin levels and rate of infections are secondary endpoints in 2201 Part II and are compared in the indirect treatment comparison to support the real-world effectiveness and

long-term use of leniolisib. Evaluation of serum IgM in 2201 Part II showed a mean decrease of 208.26mg/dL in leniolisib compared to 10.00 mg/dL in placebo from baseline to week 12 and improvement was sustained during 2201 E1 to Day 252 (~8 months) with mean levels falling within the normal reference range as defined by Van Gent et al 2009 and Morbach, 2010,[28,29] (see Figure 11 of the CS[14]). Whilst this sustained reduction in IgM supports improvement in immunophenotype, secondary endpoints are suggestive, and any statistically significant results from post-hoc analysis should be interpreted with caution. Annualised infection rates were lower in participants treated with leniolisib compared to the placebo group (2.690 versus 3.476 infections per year). Please refer to section 4.3 below to see the critique of the indirect treatment comparison.

4.2.2.4.3 Patient relevant outcomes

HRQoL

There are no validated HRQoL measures for APDS. Therefore, HRQoL was assessed using both the SF-36 (v2) and Patient Global Assessment (PtGA) as pre-specified secondary endpoints in 2201 Part II and E1.

No meaningful change from baseline (CfB) was observed in the leniolisib group across any of the eight SF-36 scales in 2201 Part II or I. Additionally, there was no statistically significant difference in the physical or mental component summary scores CfB between treatment arms at week 12 (n=27). When considering long-term follow up data from 2201 E1 there was a mean CfB (SD) at the longest reported time period 208 weeks (~48 months) in three out of eight scales, which exceeded the within-participant meaningful change thresholds for SF-36 domain norm-based scores (see Table 29 of the CS):

- Physical function: mean CfB 5.36 (SD=4.95, n=10).
- General health: mean CfB 9.79 (SD=5.46, n=10) and improvement in this scale was consistent across all timepoints (Week 12, 52, 130, 156).
- Vitality: mean CfB of 10.1 (SD=7.16, n=10).
- Data for the physical and mental component summary measures are not reported for week 208 but data for physical component score (PCS) does show improvement at weeks 12 and 52. PCS mean CfB at 52 weeks was 5.49 (SD=7.28, n=28).

In summary, SF-36 data from 2201 Part II is limited and open-label study data show consistent improvement in general health up to 208 weeks and some improvement in physical component summary measures at both 12 and 52 weeks.

Some improvement in PtGA scores in those receiving leniolisib compared to baseline in 2201 Part II were reported as being within the participant meaningful change threshold (10-20mm) (see section B.2.6.7 of the CS for further explanation). A mean CfB at week 12 for leniolisib was reported as 13.05mm (SD=20.71, n=19) compared to placebo -2.25mm (SD=28.95, n=8, there was no statistically significant difference between the treatment groups (p=0.2113). Long-term mean CfB at Week 208 in Study 2201E1 was 25.63mm points of improvement (SD=26.62, n=10); results for all time points, weeks 12, 182 and 208 were described as generally being greater than the meaningful change threshold of >10mm.

Fatigue

Fatigue (or increased energy levels) was noted as an important outcome by all patients (n=6) in Part I, leading to its inclusion as an exploratory outcome in version 7 (July 2017) of the Part II protocol, measured by tri-axial accelerometer. However, the CS indicates that fatigue was not formally measured as an outcome *per se* during the clinical trial programme and was instead documented through investigator-reported narratives collected at the end of 2201 Part II. Investigator narratives describe positive improvements, with 70% of participants receiving leniolisib reporting increased physical activity tolerance and decreased fatigue

compared to 44.4% receiving placebo. Given the importance highlighted by patients, a direct patient-reported measure of fatigue may have provided more informative data rather than the clinician's impression. Further, the sample size is not reported, and the data capture is potentially subject to recall bias. A published case series with six years of follow-up data reported five out of six participants from Study 2201 E1 experienced increased physical capabilities within six months and improved socialisation within one year of leniolisib treatment,[30] this supports qualitative data provided in section B.2.6.5 of the CS. [14] Additionally, data from the EAP reports that 53.0% of affected individuals had clinically meaningful improvements in chronic fatigue, with 27.0% of affected individuals achieving remission.[31]

4.2.2.4.4 Adverse events

Across the clinical trial programme, the adverse events (AE) and treatment emergent adverse event (TEAEs) reported in participants who were administered leniolisib were classified as follows: 82.0% (433/528) were Grade 1-2 and 10.0% (53/528) were Grade 3-4.

SAEs

In 2201 Part II, 20.0% (2/10) of participants on placebo reported six SAEs, compared to 14.3% (3/21) treated with leniolisib who reported five SAEs. In 2201 E1, 21.6% (8/37) of participants experienced 36 treatment-emergent SAEs. The most frequently affected system organ class for SAEs was infections and infestations (13.5% (5/37)) and gastrointestinal disorders (8.1% (3/37)). The investigator considered all the SAEs reported in 2201 Part I, II and 2201 E1 to be unrelated to leniolisib.

Discontinuation

Across the clinical trial programme, six people (16.2%) discontinued treatment. All were enrolled in 2201 E1 (n=37). Reasons include death, adverse event, physician decision, participant/guardian decision (all n=1), and study termination by sponsor (n=2). See CS for more information. The EAG asked the company to clarify the plausibility of classical Hodgkin Lymphoma in a larger sample size. The company responded that this AE was not considered to be related to leniolisib, by the investigator. Including data from the global EAP with over 200 years of exposure to leniolisib seven individuals with APDS have discontinued treatment. See company response to PfCs for more information.

Deaths

[redacted] deaths occurred in the trials; [redacted] completed 2201 Part II [redacted] prior exposure to leniolisib; [redacted] leading to discontinuation and then death. [redacted] were considered unrelated to the study drug.

4.3 Critique of trials and data identified and included in the indirect comparison

The company carried out an indirect treatment comparison to provide evidence about leniolisib compared to standard care (to add to the evidence from the RCT about leniolisib compared to placebo). The treatment arm included patients in the extension study,[25] and the control arm comprised eligible patients from the ESID study registry who were receiving more representative standard care.

A summary of the EAG's critique of the design, conduct and analysis of Study 2201 Part II is presented in Table 18.

Table 18: Summary of the EAG's critique of the ITC methods

Aspect of analysis design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	Appendix N.2, pg. 244;[19] Whalen (submitted 2024)[32]	**Appropriate** The company conducted a comparative analysis using treatment data from patients in the single-arm extension trial and control data from eligible patients in the ESID registry. This is an appropriate way to compare leniolisib to standard care, where the trial control group contained patients receiving placebo and not standard care. The company carried out inverse probability of treatment weighting (IPTW) analyses to adjust for baseline differences between these samples. This is an appropriate method to use in this context, where there is individual patient data (IPD) available for both arms of the study.
Included study characteristics and demographics	Appendix N.1.3 table 98, pg. 228[19] Appendix N.2.2 pg. 244[19]	**Some concerns** The treatment group was taken from the extension trial, and the control group was taken from registry data. Similar eligibility criteria were applied to both groups except that the age and weight criteria were not applied to the control group. See section 4.3.1 for further details.
Covariates included and excluded in the IPTW	Appendix N.2.2 pg. 245;[19] Whalen (submitted 2024) pg. 8[32]	**Appropriate** For the respiratory infections analysis, the company included age, IRT use at baseline, and baseline infection rate. For the serum IgM analysis, the company included age, sex, baseline serum IgM levels, and APDS mutation status. The EAG asked the company to provide their rationale for the selection of covariates in each analysis and agreed with these rationales.
Weighting of covariates	Whalen (submitted 2024)[32]	**Some concerns** IPTW analyses were not always successful in achieving balance between the treatment and control groups for all baseline characteristics. In addition, some covariates were not included in the IPTW analyses, which may have influenced the outcomes; see section 4.3.2.
Outcomes	Appendix N.2.2 pg. 244-5[19]	**Some concerns** The company analysed i) incidence of respiratory infections and ii) change in serum IgM values. These are clinically appropriate outcomes and included in the NICE decision problem.

		The EAG has some concerns about the follow-up time, which are expanded in section 4.3.3.
Results	Appendix N.2.2. pg. 246;[19] Whalen (submitted 2024) Figure 1, pg. 12; Figure 2, pg. 15[32]	**Some concerns** The company reported a statistically significantly lower rate of respiratory infections in the treatment group, with a rate ratio of 0.34 (95% CI 0.19 to 0.59) for leniolisib versus standard care. The company reported that the treatment group experienced a difference in median annualised change in IgM of -1.09 g/L (95% CI: -1.78 to -0.39, p=0.002) compared to the control group (i.e. leniolisib reduced serum IgM more than standard care). The company stated that the indirect comparison provided results consistent with the RCT.
Sensitivity analyses	Whalen (submitted 2024) pg. 12 + 15[32]	**Appropriate** The company reported sensitivity analyses that explored the impact of incorporating different data and covariates, and reported that the results were consistent across the analyses. The EAG's concerns about the sensitivity analyses are reported in section 4.3.4.
Abbreviations: APDS = activated phosphoinositide 3-kinase delta; CS = company submission; EAG = Evidence Assessment Group; ESID = European Society for Immunodeficiences; HSCT = hematopoietic stem cell transplantation; IgM = immunoglobulin M antibody; IPD = individual patient data; IPTW = inverse probability of treatment weighting; IRT = immunoglobulin replacement therapy; PI3KCδ, PIK3R1 = types of phosphoinositide 3-kinase delta		

4.3.1 Included study characteristics and demographics

For the treatment group of the ITC, participants from part I (dose finding study) and part II (RCT) were eligible plus two further patients: aged 12-75 years with documented APDS-associated pathogenic gene variant in PIK3CD (APDS1) or PIK3R1 (APDS2) and lymphoproliferation.

For the control group, the company included eligible participants from the ESID registry which is the largest registry of individuals with primary immunodeficiencies worldwide. Patients were excluded if they had only one registry visit, or if they received an alternative PI3Kδ inhibitor or HSCT prior to or on the second visit. Participants from the ESID registry did not have the same eligibility criteria applied as patients entering the trials: there was no restriction by age or weight and younger patients were included in the control group (median age 12 years [IQR 7 to 21]). Control patients were not required to have lymphoproliferation at baseline and 17% did not.

4.3.2 IPTW Analyses

4.3.2.1 Respiratory infections analysis

Baseline differences remained after the IPTW analyses for receipt of IRT, serum IgM, baseline infection rate and APDS type.[32] (Table 1, pg. 10). Control group patients were more likely to have received IRT at baseline, which may lead to an underestimate of the effectiveness of leniolisib. Baseline infection rate was higher in the control group, which may lead to an over-estimate of the effectiveness of leniolisib, although the absolute number of

infections was low. Clinical advice to the EAG suggested APDS type was unlikely to be a prognostic factor, therefore baseline differences were of less concern.

Use of steroids was not included in the IPTW analyses and was more common in the treatment population. Given that steroids target immune dysregulation by inhibiting leukocyte activity and proliferation, this could lead to an overestimate on the effectiveness of leniolisib.[32] (Table 2, pg. 11)

Use of mTOR was considered in the IPTW analyses. However, there were no patients on mTOR in the treatment population, which consisted of patients from the clinical studies. In contrast, 37% of control participants were receiving mTOR at baseline, and 44% at follow-up. . Given that mTOR has been reported as effective in treating lymphoproliferation, this could make leniolisib appear less effective. However, since leniolisib is considered to be an alternative the use of these medications, higher rates of mTOR use are expected in the control group. The company did not include steroid use or mTOR use in the sensitivity analyses.

4.3.2.2 Serum IgM analysis

Baseline characteristics were similar between groups after the IPTW analyses were conducted.[32] (Table 3, pg. 13) However, infections at baseline were not included in these analyses, therefore baseline differences remained.[32] (Table 4, pg. 14)

4.3.3 Outcomes

4.3.3.1 Respiratory infections analysis

For the treatment group eligible infections included otitis media, sinusitis, bronchitis, infective exacerbation of bronchiectasis, respiratory tract infection and pneumonia; for the control group they included otitis media, sinusitis, chest infection and pneumonia because this was the infection data reported in ESID.

4.3.3.2 Serum IgM analysis

The serum IgM outcomes were annualised to account for the fact that there was a longer interval between measurements in the control group than the treatment group. As the median interval between the first and last IgM tests recorded in the treatment population was 254 days, results were considered to be the rate of change per year, without adjustment.

4.3.4 Sensitivity analyses

4.3.4.1 Respiratory infections analysis

Sensitivity analyses for the respiratory infections analysis explored the impact of: i) imputing missing values rather than using complete cases only, ii) using data from partI/II versus the extension trial, iii) including serum IgM, sex and APDS type as covariates as well as age and baseline IRT and infections, and iv) not censoring at HSCT.

4.3.4.2 Serum IgM analysis

Sensitivity analyses for the serum IgM analysis explored the impact of: i) different time points of measurement (e.g. first to lowest or first to last instead of first to second measurement), and ii) not censoring for HSCT.

For both analyses, the company reported that the results were consistent across the analyses. They did not report a test for differences although visual inspection of the forest plots supports this assertion.

4.4 Summary of all company evidence for leniolisib

4.4.1 Methods

The company evidence to evaluate the safety and efficacy of leniolisib in people with APDS comprises:

- a 12-week, open-label, dose-finding study (2201 Part I)
- a 12-week, randomised, triple-blind, placebo-controlled phase III trial (2201 Part II)
- an ongoing, open-label extension study (2201E1)
- an indirect treatment comparison which uses extension study participants as the treatment arm and eligible ESID registry patients as the control arm.

In total, 38 people received treatment in the clinical trial programme, and an additional 72 people have received leniolisib via the EAP, including six people from three participating centres in the UK.

Study 2201 Part I (n=6) was conducted over 12 weeks establishing an optimal dose of 70mg bid and confirming safety and pharmacokinetic profiles. The EAG has no major concerns about the conduct of Part I.[8]

Study 2201 Part II (n=31) appears to have been methodologically sound although some areas, such as concealment of allocation, were at unclear risk of bias.[22] The key issue is that the comparator group did not receive established clinical management as understood in the UK and defined in the NICE scope. Instead they received a placebo plus restricted symptomatic management but immunosuppressants were prohibited, which may have over-estimated the apparent effectiveness of leniolisib. Also, there were imbalances in baseline clinical characteristics, which indicate patients randomised to placebo were more severely impacted at baseline, potentially overestimating any treatment effects. Post-hoc identification of clinically meaningful thresholds was undertaken to determine the proportion of responders to leniolisib. It is unclear how reliably the co-primary surrogate outcomes (specifically, proportion of naïve to total B cells) predict long-term clinically relevant outcomes that reflect a benefit to patients, but the company reasoned that variability in clinical outcomes is large and the sample size would have had to be unreasonably large to have clinical outcomes as primary outcomes. The small sample size is appropriate relative to the estimated number of people known to have APDS. The trial was conducted across ten sites in nine countries, including Belfast in the UK and the EAG is satisfied the results are generalisable to patients in England and the UK.

Study 2201E1 is an ongoing open-label, multicentre, single arm extension study over six years and three months, for participants who participated in Part I or Part II, or who were treated previously with other PI3Kδ inhibitors and fitted study eligibility criteria.[25] It aimed evaluate longer term safety, tolerability, efficacy and pharmacokinetic data over six years. The EAG has no major concerns about the conduct of 2201E1.

Finally, the company conducted an indirect treatment comparison to assess external validity. This analysis compared participants from the 2201E1 extension study to eligible control participants from the ESID registry, providing a more generalisable standard care group compared to that in 2201 Part II.[32] However the eligibility criteria for the treatment and control group were not matched as there was no age or weight restriction for control participants from the registry. The EAG has some concerns because the weighting across arms was not successful for the respiratory infections analysis.

4.4.2 Results

Because this is an active area of evolving research, many aspects of the study appear exploratory. While treatment with leniolisib appears to demonstrate improvement in many

parameters, there is a risk measuring many outcomes and endpoints and analysing them in different ways can lead to chance findings.

Overall, leniolisib appears to be generally well tolerated across the programme, with a median exposure of three years. Most of the AEs/TEAEs were grade 1-2. None of the TEAEs that were reported during 2201 or E1 lead to discontinuation (n=6; 2201 E1). In addition, though there were [redacted], investigators determined they were unrelated to the study drug. The EAG is satisfied that these events are fully reported in documentation provided by the company.

The company reported a statistically significant effect on the co-primary surrogate endpoints, indicating immunophenotype normalisation and reduction in lymphoproliferation maintained across all trials to the interim analysis cut-off in the extension trial.

Results from the indirect treatment comparison show improvements in the more clinically relevant outcomes of serum IgM levels and respiratory infection rates consistent with findings from 2201 Part II.

Findings on quality of life from the SF-36 data were limited and, in the EAG's view, did not demonstrate long-term improvement in health-related quality of life, with the exception of the general health scale. Findings from PtGA scores were more favourable, as were participant narratives collected during 2201 Part II. All participants from Part I mentioned fatigue as important to them; in the EAG's view, a more robust measure of fatigue would have provided better patient-relevant data.

5 COST EFFECTIVENESS

5.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

Table 19 presents an overview of the EAG's critique of the methods used to identify studies for the review of cost-effectiveness.

Table 19: Summary of the EAG's critique of the methods for the review of cost-effectiveness

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Data sources for cost-effectiveness analysis review	Appendix G.1, p 163-173 Appendix D.1.1, p 14-18	**Some concerns** An appropriate range of databases and grey literature sources were used in the original 2021 SLR and the 2023 update but some sources were omitted in the targeted 2024 SLR.
Search strategies	Appendix G.1, p 163-173	**Some concerns** Bibliographic database searches failed to include previous MeSH subject headings used for indexing Phosphatidylinositol 3-Kinases such as Phosphotransferases/ and "Phosphotransferases (Alcohol Group Acceptor)"/ which could have led to missing relevant literature. The 2021 searches present some differences to the text search terms and the MeSH subject headings used in the subsequent 2023 and 2024 updates although this is not considered a major concern due to the method for de-duplication used.
Search Filters	Appendix G.1.1, p 164-171	**Some concerns** A search strategy for identification of health economic studies was used appropriately in relevant databases. The company did not provide information of the origin of the cost-effectiveness filter and the EAG queried this in the PfC letter which the company responded to on PfC response (Section B.1, pg. 36). For an EAG critique of the methods see section 5.1.1.2
Data sources for model input	Appendix P, p 273 - 274	**Some concerns** A targeted search for proxy utility values was performed. The CS did not provide information on the sources searched, date searched, or number of records retrieved. The EAG queried with the company in the PfC letter, and the company responded on the Response PfC letter (pg. 51-52). An overview of the EAG critique on the methods is included in section 5.1.1.3
Eligibility criteria for inclusion of economic evaluations		Appropriate
Eligibility criteria for inclusion of health state utility value studies		Appropriate

Eligibility criteria for inclusion of resource use and cost studies		Appropriate
Abbreviations: CS = company submission; EAG = Evidence Assessment Group		

5.1.1 Search strategies for cost-effectiveness SLR

Searches were conducted separately for economic studies (cost-effectiveness and cost resource use) and HRQoL (Appendix H). Searches were appraised by the EAG using the Peer Review of Electronic Search Strategies (PRESS) checklist.[18] Searches were conducted from the inception date of databases until 11th November 2021, and updated in May 2023, and again in April 2024 so they can be considered up to date. The EAG's critique of HRQoL searches are in Section 5.2.6.1 while the EAG's critique of the way the use of previous MeSH headings were omitted in all searches (clinical effectiveness, economic, and HRQoL) can be found in Section 4.1.1.2.

5.1.1.1 Sources

The company searched a reasonable range of databases and grey sources: MEDLINE, Embase, The Cochrane Library databases (CENTRAL and Database of Systematic Reviews), CRD databases (DARE, NHS EED and HTA Database), EconLit and ScHARRHUD (School of Health and Related Research Health Utilities Database). For the EAG's assessment of conference sources used in the CS, see Section 4.1.1.1.

In the CS (Appendix G, Table 45, p 173-174) the company describe searching additional grey sources (CEA Registry and EQ-5D) for the SLR update in 2023 only. The EAG note that these searches were not reported in the PRISMA flowchart for cost-effectiveness (Appendix G, Figure 2, p 178). Furthermore, the company performed a targeted search in 2024 where it did not search comprehensively all sources used in the original SLR 2021 and update SLR 2023.While justification is provided for some of the sources not used in the 2024 targeted search, the company does not provide justification for not searching EconLit in the SLR 2024. The implications of not searching systematically all sources are mainly the introduction of potential publication bias.

5.1.1.2 Search filters

Searches were restricted to economic studies using a set of search strings (referred here as 'filter') in combination with the main clinical-focussed concepts. The EAG has not been able to identify if the company used a validated and published filter. The EAG queried this with the company in the PfC letter (B1. p 7) and the company responded in the PfC response (B1. pg.36).[26] The EAG understands that the company developed its own cost-effectiveness filter from two established and validated filters used by The Scottish Intercollegiate Guidelines Network (SIGN) and the Canadian Agency for Drugs and Technologies in health (CADTH). The company has not provided a justification for the need of developing a new filter and, in comparison with the existing cited filters, the EAG can only identify very little similarities. The company removed many cost-effectiveness related lines from the existing filter and replaced them with new lines of search terms in controlled vocabulary and free text. The company has not provided a rationale for this change and the EAG is not able to test if this approach would have resulted in a more or less sensitive strategy for the retrieval of relevant studies.

Without comprehensive testing, it is difficult for the EAG to quantify the effects that all the issues mentioned may have had on search results, but it seems likely the effects would be

relatively minor. Overall, the EAG is satisfied that the search for economic studies was conducted appropriately.

5.1.1.3 Proxy searches for model input

In the response to PfC letter (B6. pg. 51-53) the company discloses a two-phase approach to identifying studies for model input values.[26] Phase one maps to the reported searches and number of included studies in CS Appendix O – Targeted search for proxy utility values (pgs. 253-254).[19] However, phase two was only disclosed in the response to PfC after the EAG raised a query about the methods for identification and selection of studies to populate the model. In this phase a different method to identify relevant studies which mainly consists of expert consultation for the selection of proxy conditions validated by existing previous NICE technologies appraisals is introduced.

The company cites that "*To ensure consistency with prior technology assessments, studies cited in previous NICE technology appraisal were given priority for selection as inputs, over some of the data identified in the Phase 1 searches*" (Response to PfC, pg. 52). [26] The company accompanies this explanation with Table 18 (Response to PfC, pg. 52) in which lists all included studies from the second phase.[26]

Furthermore, phase one only used PubMed as the main source for searching and only included open access studies which would have introduced publication bias in the selection of studies for inclusion. Phase two depends on studies included in previously published NICE technology appraisals.

Both methods present limitations in their own rights that could bias the selection of studies. A systematic literature search would have been the preferred method for the identification of current proxy values. Without further testing the EAG is not able to ascertain the implication of the methods used for the overall model input and results.

5.2 Summary and critique of company's submitted economic evaluation by the EAG

5.2.1 NICE reference case checklist

Table 20 summarises the NICE reference case checklist and the EAG's assessment on the company's submission in relation to their base-case analysis. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 20: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	From the scope: People with activated phosphoinositide 3-kinase delta syndrome 12 years and older.	**Some concerns** The model considers adults 15 years or older. The company justifies this decision as this was the average age of people with APDS in the Level 1 (mandatory) dataset of the ESID registry (November 2023 dataset). The summary ESID information submitted by the company states however that the mean age at registry is 17.7 See section 5.2.2.1 for further details.
Comparators	From the scope: Established clinical management without leniolisib	**Appropriate** After consultation with clinical experts, the treatment of APDS varies considerably as each individual has different needs. This makes it difficult to consider what established clinical management looks like. The approach considered by the company was including a combination of antimicrobials, immunoglobulin replacement therapy (IRT), immunosuppressive therapies (including steroids, rituximab and mammalian target of rapamycin [mTOR] inhibitors), haematopoietic stem cell transplantation (HSCT), surgery and other procedures was considered appropriate by the EAG.

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	Outcomes measured in the final scope included: Infections • Lung function • Fatigue • Mortality • Disease severity • Immunophenotype measures (lymphocyte counts, immunoglobulin levels, cytokine and chemokine levels) • Immune system function (lymph node size, spleen and liver volume size, use of immunoglobulin replacement therapy) • Adverse and serious effects of treatment • Health-related quality of life.	**Some concerns** Outcomes included in the cost-effectiveness model were: • Mortality • Incidence rates for various manifestations of APDS and treatment use under current clinical management • HRQoL for proxy conditions measured in QALYs The model does not include adverse effects. See section 5.2.5 for further details.
Perspective on costs	NHS and Personal Social Services (PPS) perspective.	**Some concerns** The EAG note that the company has taken an NHS perspective, not an NHS and PPS perspective. The company confirmed this in their PfC response. See section 5.2.2.2 for further details.
Type of economic evaluation	Cost-utility analysis with a fully incremental analysis.	**Appropriate** The company presented a full cost-utility analysis comparing leniolisib with current clinical management
Time horizon	Long enough to reflect all important differences in costs and outcomes between the technologies being compared.	**Appropriate** A lifetime horizon was used for the cost-effectiveness analysis.

Element of health technology assessment	Reference case	EAG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review.	**Appropriate** The company conducted a systematic search on HRQoL (health-related quality of life) with insufficient information about the search filter used. The company then did a search on proxy conditions without revealing details of the databases, they searched, total number of records retrieved and date the search was performed; these details were provided at the clarification stage (Question B6). [26] See section 5.2.6.1 for further details.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Some concerns** EQ-5D based utilities with UK value set were not always used for the proxy conditions. See section 5.2.6.3 for further details. **Some concerns** The company applied a QALY weight of 1.5 to the discounted Incremental QALYs in the base case analysis. the EAG believes that the application of this weight is not in line with NICE guidelines.[1] See section 5.2.2.4 for further details.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by the patients or carers or both.	**Some concerns** Due to lack of evidence on HRQoL measured for APDS, utility for proxy conditions were used. The use of proxy conditions can provide inaccurate estimates of the impact of APDS on HRQoL and may complicate the utility calculation process in CEM (cost effectiveness model). See section 5.2.6.2 for further details.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	**Some concerns** The baseline utility was elicited through clinician valuation survey. The utility values derived from the studies of proxy conditions were not always a representative sample of the UK population. See section 5.2.6.3 for further details.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances.	**Appropriate** There was no indication of unequal weighting given to individuals.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	**Some concerns** Costs and resource use mostly sourced from NHS reference costs, [33] BNF[34] and eMIT.[35] The EAG were not able to verify some of these costs which leads to uncertainty surrounding the total costs included in the model. Furthermore, the EAG prioritised eMIT as the preferred source of unit costs whenever possible as per section 4.4 of the NICE HTE manual. [1] See section 5.2.7.1 for further details.

Element of health technology assessment	Reference case	EAG comment on company's submission
Discounting	The same annual rate for both costs and health effects (3.5%)	**Key issue** The company applied a discount rate of 3.5% to costs and 1.5% to QALY gains which the EAG considers a deviation from the NICE reference case [1] See section 5.2.2.3 for further details.
Abbreviation: EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence		

5.2.2 Decision problem

Table 21 summarises the EAG's critique on the decision problem of the model adopted by the company.

Table 21: Summary of EAG's critique on the decision problem

Aspect of model	Section in CS where methods are reported	EAG's assessment
Defining the decision problem and population	Document B.3.3.1, p. 132; Pharming_ESID Registry Analysis Summary Document_NICE_22May2024[36]	**Some concerns** The economic model includes adults 15 years or older. The company justifies this decision as age 15 is the average age of people with APDS in the APDS in the Level 1 (mandatory) dataset of the ESID registry (November 2023 dataset). The summary ESID information submitted by the company states however that the mean age at registry is 17.7. [36] See section 5.2.2.1 for further details.
Perspective	Document B.3.5, p. 162	**Some concerns** The EAG note that the company has taken a partial perspective (NHS only). No Personal Social Services costs have been added to the model. See section 5.2.2.2 for further details.
Time horizon	Document B.3.2.2, p. 127	**Appropriate** Lifetime
Discounting	Document B.3.2.2, p.131	**Key Issue [1]** The company applied a 1.5% discounting for health effects and 3.5% discount for costs, which is inconsistent with recent NICE guidelines.[1] See section 5.2.2.3 for further details.
QALY gain weighting	Document B.3.9.1, p.175	**Some concerns** The company applies a 1.5 QALY weighting in the base-case deterministic results and uses the produced cost-effectiveness results in the conclusion of this submission. EAG thinks the presentation of results is unclear. See section 5.2.2.4 for further details.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group		

5.2.2.1 Defining the decision problem and population

The economic model was run for a cohort of individuals starting treatment at age 15. The company justifies using 15 as this is the average age of people with APDS registered in the Level 1 dataset of the ESID registry (November 2023 dataset).[36] However, this is inconsistent with the information in the summary results of ESID submitted by the company, which states that the mean age at registry is 17.7.[36] Therefore, the EAG could not verify the appropriateness of the starting age assumption given the inconsistent statement between submitted documents. In order to test this assumption and its potential effect on cost-effectiveness, the EAG have included a sensitivity analysis which assumes the starting age for the cohort of individuals to be 18 years old.

5.2.2.2 Perspective

With respect to costs the EAG note that the CS adopted an NHS perspective deviating from the NHS and PSS perspective in the NICE reference case. The company has confirmed in their PfC response that the cost-effectiveness analysis presented in the CS adopted an NHS perspective (and not a PSS perspective). Costs were confined to the use of primary, secondary and tertiary care services associated with the monitoring and treatment of the manifestations associated with APDS, even though the costs falling on PSS were stated as having been included in the analysis. Subsequently, the company confirmed in their PfC response that the cost-effectiveness analysis presented in the CS adopted an NHS perspective only (and not a Personal Social Services perspective). Given the burden of this condition on activities of daily living, educational and employment outcomes, the EAG considers the burden on Personal and Social Services should have been considered.

5.2.2.3 Discounting

In the summary of the cost-effectiveness analysis (Section B.3), the company states that a 1.5% discount rate for the future health effects was used in their base-case analysis as "leniolisib is expected to be prescribed from age 12 years and is expected to provide substantial and sustained benefits to the quality and length of life of people with APDS."[14] The recent NICE HTE manual recommended a 3.5% discount rate for both costs and effects.[1] The manual states three exceptions when alternative discount rates are acceptable, with all criteria needing to be met: 1) The technology is for people who would otherwise die or have a very severely impaired life; 2) It is likely to restore them to full or near-full health; 3) The benefits are likely to be sustained over a very long period.[1] It is in the EAG's view that the technologies does not sufficiently meet these three criteria.

The EAG asked the company to clarify how the above criteria are met for this HST and therefore to provide further justification regarding the use of a 1.5% discount rate for future health effects. The EAG also requested the company to conduct the base-case analysis using the 3.5% discount rate if they think their submission is unable to meet the NICE criteria [1] stated above. The company has provided justification on the use of the 1.5% discount rate and this is included in their PfC response.[26]

Overall, the EAG agree that the effectiveness evidence submitted by the company suggests that leniolisib substantially decreases the rate of manifestations associated with APDS, alleviate the symptom burden on patients. The company's own elicitation exercise suggest that it may subsequently lead to significant improvements in QoL and life expectancy. However, the EAG also note that there is uncertainty in the effectiveness and duration of leniolisib. First, the drug appears not to eliminate manifestations in all patients from the current clinical evidence. In addition, due to the lack of long-term data and the mean age of participants starting treatment (15 years old in the economic model) it remains unclear whether participants would regain full health or near full health. Finally, the lack of longer term data means that uncertainty remains on whether the benefits are likely to be sustained over a very long period. The EAG hence note uncertainty remains on whether the criteria set by NICE for the application of alternative discount rates is jointly and fully met. The EAG therefore recommend that a 3.5% discount rate is applied to both costs and effects in the base-case analysis. However, the EAG note that the decision whether to apply an alternative discount rate of 1.5% is the responsibility of the committee. Therefore, the EAG applied a 3.5% discount rate to both costs and effects in EAG's own base-case analysis and conducted a sensitivity analysis using the 1.5% discount rate for the both the costs and health effects.

5.2.2.4 QALY gain weighting

The company applied a 1.5 weight for the QALY gain to the deterministic and probabilistic analyses based on the undiscounted QALY gains derived from their economic analysis comparing leniolisib with current clinical management. The EAG requested the company to

provide further clarification regarding whether the application of the QALY weight to the company's base-case analysis is consistent with the NICE HTE manual.

The NICE HTE manual indicates that "*For highly specialised technologies, the committee will consider the size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of the technology to fall within the highly specialised technologies £100,000 cost per QALY level"* (section sections 6.2.23, NICE HTE manual[1]. The NICE HTE manual further defines the qualifying criteria for the potential application of a QALY gain weight saying that "*For this weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained" (section sections 6.2.24, NICE HTE manual[1]).*

The EAG acknowledge that the company's undiscounted base-case QALY gains are sizeable and adhere to the criteria set by NICE for highly specialised technologies. The EAG also agrees with the company that the current NICE manual does not comment on whether undiscounted or discounted QALYs should be used to calculate the QALY weight. However, following recent NICE HST evaluations, the use of undiscounted incremental QALYs to calculate QALY weights seems appropriate.

Nevertheless, the EAG believe that the calculated QALY weight should not have been applied to the company's base-case analyses. Based on the NICE HTE manual, it is up to the committee to discuss the weight it attaches to the results of a non-reference case analysis. The committee should then consider whether the application of the suggested QALY weight is appropriate.[1]. The EAG recommend presenting the unweighted CE results alongside with a recommendation of the QALY gain weight that could be applied if the incremental undiscounted QALY gain is bigger than 10.

The EAG recommendation is supported by recently submitted HSTs (e.g., HST30[37]) where QALY weight results have been submitted as part of the submitted exploratory analysis as well as by past NICE guidance on the evaluation of highly specialised technologies that states that *The Committee will consider the size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost-effectiveness of the technology to fall within the HST £100,000 QALY limit. Although the NICE website indicates that this past document* only applies to appraisals that started before 1 February 2022, the EAG note that no change in guidance specifically applicable to highly specialised technologies has been subsequently published by NICE.

5.2.3 Model structure

Table 22 summarises the EAG's critique on the model structure and inputs adopted by the company.

Table 22: Summary of EAG's critique on the design of the economic model

Aspect of model	Section in CS where methods are reported	EAG's assessment
Type of model	Document B.3.2.2, p.127	**Appropriate** The EAG notes that a limited number of UK- based clinical experts were involved in the model (pathway) validation process, yet acknowledges the availability of clinical experts in this rare field and the structured expert elicitation process the company has organised. See section 5.2.3.1 for further details.
Health states/events and transitions	Document B.3.2.2, p.126-130	**Appropriate** The model has three states: alive on leniolisib treatment; alive not on leniolisib treatment and death. Within each alive health state, the manifestation incidence and prevalence and treatment utilisation were estimated using a partitioned approach.
Modelling Uncertainty	Document B.3.10.1, p.177	**Key Issue [2]** In the probabilistic sensitivity analysis, the company assumed standard error to be 10% of its mean for parameters where uncertainty information was not available. However, the assumed level of uncertainty sits at the lower bound of many HTA studies[26] without justification. See section 5.2.3.2 for further details.
Survival analysis and extrapolation methods	Document B.3.3.3, p.137; Document B.3.3.4, p.149-150;	**Appropriate** Overall survival in the current clinical management arm was informed by a Weibull curve fitted to KM data from the patient-level data obtained from systematic literature review.[38] Clinician's views were used to validate the resultant survival curve. Impact of treatment on survival (represented by a hazard ratio) in the leniolisib arm was informed by clinicians' views given that the effect of leniolisib on mortality was not assessed in the trial. Please see section 5.2.4.2 for further details of EAG'S comments on the impact of treatment on survival
Abbreviations: CS = company submission; EAG = Evidence Assessment Group		

5.2.3.1 Justifications on the type of model structure

The company mentioned that "the final model structure was chosen to reflect key characteristics of APDS and data availability, and was validated by three HTA experts and one UK clinical expert." [14] In the Expert Consultancy (Exercise 3), another three UK clinicians were presented with a diagram containing all of the treatments used in the company's economic model, and agreed that the diagram represents their region's treatment patterns for patients with APDS. [39] The company clarification response included a summary of the expert elicitation process, with details provided, for example, about the identification of

topics and post interview follow-up. The EAG understands that virtual, semi-structured interviews were conducted to validate a number of assumptions including potential modelling approaches/assumptions. The company confirmed the attendance and the contribution of the UK clinical expert in the interview. Agreement was reached on assumptions related to the model structure, which includes (a) modelling the APDS patient population as a whole (not differentiating between APDS1 and APDS2 patients); (b) use of age-dependent cohort level Markov model so it allows the model to track the average age-dependent onset of multiple, key manifestations in line with the progressive nature of APDS; (c) accounting for combinations of manifestations across multiple organ systems in one patient, by modelling each manifestation separately and using an aggregation approach in the calculation of disutility caused by manifestations.

Overall, the EAG acknowledge that the availability of clinical experts in this field would have been limited and that the chosen model structure was justified using an organised elicitation process. Other efforts have been done to justify the use of the current model structure. For example, a SLR has been conducted to search economic evaluations studies in APDS but no published economic models were found. Another search was conducted to identify relevant evidence in other disease areas, and similar approaches for modelling multiple manifestations. Alternative model structures and their drawbacks were discussed in the CS (Section 3.2.2, p.127-128).[14]The EAG therefore considers the company's choice of model structure appropriate.

5.2.3.2 Modelling uncertainty

In the probabilistic sensitivity analysis section (Doc B B.3.10.1, p177), the company stated that "Where empirical probability distributions were not available, the standard error was assumed to take a value equal to 10% of that of the mean."[14] The EAG note that most of the key model parameters for utility, costs and hazard ratios (HR) for the incidence rates of manifestations used a 10% standard error to represent variation in the precision of model parameters in the model.[19] The EAG requested the company to justify the use of the 10% SE in the PSA. The company provided evidence from a review of all full NICE single TAs published in 2013-2014.[3] The review focused on the assessment of the appropriateness of the PSA conducted in the identified TAs and whether the approaches adopted conformed to the relevant guidelines.[3] The company cited one of the findings of this review that "The variation for the parameters was in most cases assumed and not informed by data, with 68% of TAs including at least one parameter where the standard error was assumed to be 10–30% of the mean, with 20% being the most common assumption."[3]

The EAG acknowledge that the company's 10% SE assumption is within the range of the 10-30% from the review. However, this doesn't justify (a) the company's choice of 10%, which is the lower bound of the range, which implies a high level of precision (and therefore certainty) about the estimate, this level of precision does not appear appropriate given that these estimates were not based on directly relevant empirical evidence (the company used clinicians' judgment and proxy conditions to inform key data inputs for the model); (b) the large proportion of parameters this assumption applied to; (c) for input parameters sourced from the clinical experts, the company did not report whether they had checked that a 10% SE adequately covers the uncertainty in the expert estimates. The EAG acknowledge that the company conducted a scenario analysis in which a 20% SE was applied for parameter inputs without available information on uncertainty in the PfC.[26] The results showed that the probability of cost-effectiveness at a willingness-to-pay threshold of £100,000/QALY dropped from [redacted]% to [redacted]%, implying a moderate impact of change of scenario on CE results. The company also conducted a one-way sensitivity analysis (OWSA) in which the range of input parameters were reconstructed using a 20% SE. The results showed some changes in the Top 10 influencing parameters. The company concluded that "the magnitude of the assumed uncertainty is of less consequence for this cost-effectiveness analysis."[26]

Overall, The EAG consider a 20% SE to be more appropriate than a 10% SE given the evidence to support the parameter estimates This more conservative approach better reflects the high level of uncertainty around the estimates. The EAG used a 20% SE assumption in their probabilistic analysis and OWSA.

5.2.4 Treatment effectiveness

A summary of the EAG's view on treatment effectiveness and extrapolation is summarised in Table 23.

Table 23: Summary of EAG's critique on the treatment effectiveness

Aspect of model	Section in CS where methods are reported	EAG's assessment
Treatment effectiveness and extrapolation	Document B.3.2.2, p.132	**Key Issue [3]** The company assumed no treatment waning effect for leniolisib as there is no evidence of treatment waning across the evidence base for leniolisib (including the leniolisib trials.[22 8 25] However, the EAG's clinical experts suggested treatment waning was possible whilst noting the lack of long term data to support or refute continued efficacy. See section 5.2.4.1 for further details.
Impact of treatment on mortality	Document B.3.3.4, p.149 Document B.3.10.3, p.180-181	**Some concerns** The impact of leniolisib on survival (represented by a hazard ratio) was elicited from 4 clinicians. The EAG is concerned that some clinical experts who participated in Exercise 1 of the Expert Consultancy may have had limited experience treating APDS patients, given the ultra-rarity of the condition worldwide. **Appropriate** In a scenario analysis, the company used manifestation-specific mortality risk instead of overall survival impact of leniolisib. A calibration was conducted to ensure visual fit of the predicted survival curve to the APDS Kaplan-Meier curve in standard of care. The company elaborated the calibration approach and conducted scenario analyses using a possible range of calibration values in the document responding to EAG's Point of Clarification.[26] Overall, the EAG agrees with the company's approach to calculate manifestation-specific mortality rate. See section 5.2.4.2 for further details.
Impact of treatment on manifestations	Document B.3.3.4, p.141-147	**Some concerns** As noted above, the impact of leniolisib on some manifestations were estimated using a small number of clinical experts **Some concerns** The evidence the company used to calculate the hazard ratios for the impact of leniolisib on incidence rates of manifestations is inconsistent with the hierarchical table (Doc B, Table 41).[14] See section 5.2.4.3 for further details.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group		

5.2.4.1 The assumption of no treatment waning

The company stated that "Due to the mechanism of action (MoA) of leniolisib (as described in Section B.1.2 of the CS), a treatment waning effect was not expected. Furthermore, no evidence of treatment waning has been observed in the leniolisib clinical trials, with up to six years of published data from Study 2201E1 available [25]', and continued treatment for up to two years in the EAP [31]." In addition, an advisory board that convened with six UK experts, included focused discussion on the implications of the MoA of leniolisib, agreed that based on leniolisib's MoA, they did not foresee any likelihood of treatment response diminishing over time. One clinician also clarified that treatment effect waning in this context would be restricted to biologics (e.g. monoclonal antibodies). Therefore, there is no treatment waning effect assumed in the model. However, the EAG's clinical experts pointed out that there are no long term data to support or refute continuing efficacy over time. Therefore, it is uncertain whether the effectiveness of leniolisib will remain constant over the patient's lifetime. The EAG believes that a scenario analysis exploring the possibility of treatment waning is needed.

In the response to PfC document, the company reiterated that [redacted][40 41] and aside from poor compliance or discontinuation (in a minority of patients) there is no clinical rationale to expect loss of effect. The company then acknowledged that "the only remaining means of lost effect are discontinuation or poor adherence." The company also claimed that there was no current evidence of poor adherence, as the compliance rates were high in the trials (99%)[42] and in an observational dataset from the US market where the drug (Joenja®) was commercially available (99.3% in terms of time of a year patients complied).[14] Further to the company's response:

- The EAG note that a 3.54% treatment discontinuation has been incorporated in the company's base-case analysis of the economic model. The company stated that this discontinuation rate was sourced from their trial[25] and the EAP survey[31]).
- Having examined the clinical expert in responses to the company's own Expert Consultancy project, the EAG are concerned that the high adherence assumed by the company may be an overestimation. Responses to the survey indicated that the average proportion (%) of patients receiving a PI3Kδ-specific inhibitor expected to discontinue treatment at any point, and for any reason, is 14%. The values provided by the 5 experts surveyed range from 0% to 30%.
- The EAG acknowledge the difficulties of incorporating a potential treatment waning effect into the model, given the available evidence. The EAG have represented treatment waning in the model as total discontinuation from treatment, this has been applied via the incorporation of a higher treatment discontinuation rate based on the company's expert elicitation exercise. The EAG acknowledge that this approach has a significant limitation of excluding the cost of leniolisib treatment. The EAG have tested potential treatment waning by varying the model's discontinuation rate as follows:
    - The EAG have applied a discontinuation rate of 14% to the base-case scenario in line with the mean value derived from the company's expert elicitation exercise[39] to jointly test the impact of treatment adherence and the possibility of discontinuation due to treatment effectiveness waning
    - The EAG have conducted sensitivity analyses using the treatment discontinuation values covering the range elicited from the company's expert elicitation exercise[39] (0%, 10% and 30%).
- The EAG acknowledge that an alternative viable method to incorporate treatment waning would involve assuming that treatment waning does not necessarily lead to treatment discontinuation with people still on leniolisib despite a decrease in efficacy.

This would involve varying the effectiveness across the model cycles. Due to time constraints, this approach has not been tested by the EAG.

- The EAG note that the company has not explained how treatment discontinuation may be linked to the development of manifestations. The EAG would welcome an exploration of the relationship between treatment discontinuation and development of manifestations.

5.2.4.2 Impact of treatment on mortality

- The impact of leniolisib on survival rates

The company used clinicians' opinions to estimate the effects of leniolisib on survival, given that mortality was not assessed in the corresponding trial study.[22] Four clinical experts were asked to provide upper and lower plausible estimates for mortality at specified ages (ages 20 and 40 years) based on initiation of leniolisib at age 12 years. The experts' cumulative hazard median estimate (annualised) under current clinical management was 0.0118. Expert commentary suggested the survival curve for leniolisib should be closer to that of the general population; therefore, each expert's upper plausible estimate for long-term survival on leniolisib treatment after age 12 was used to calculate a cumulative hazard, which was then annualised, resulting in a value of [redacted] This resulted in a mean HR of [redacted] for long-term survival (with SE assumed to be 20% of the mean, i.e. [redacted]). In results validation, the company acknowledged that the annualised cumulative hazard of mortality under current clinical management using real world data (Pharming case series data) is 0.0241, which is higher than estimates based on experts' opinions. However, for consistency in the calculation and to provide a conservative estimate of survival gains for leniolisib, the company decided to adopt the upper plausible estimates of the clinical experts.

The EAG were initially not able to access the results of each individual clinicians' estimates from the modified SEE exercise and thus requested the company to provide the full detail of the survey results, which the company provided together with the PfC responses.[26] Overall, the EAG is concerned that estimates derived from a small number of experts may be subject to high levels of uncertainty. As noted by the company, the number of experts participated in the evaluation exercise is fewer than the minimum recommended by the York Centre for Health Economics reference protocol for expert elicitation.[43] Following this point, the EAG is also concerned that some clinical experts who participated in the exercise may have had limited experience treating APDS patients given the rareness of the disease worldwide, a limitation noted by the company.[39] Experience of treating patients with leniolisib is expected to be even more limited.

The EAG are concerned that the company used expert opinion in calculating annual hazard under current clinical management when real world data is available, However, the EAG acknowledged that this provides a more conservative HR estimate. In addition, the company decided to use the upper plausible range of the mortality estimates under leniolisib treatment in calculating HR estimate as one expert suggested the survival curve for leniolisib should be closer to that of the general population. The EAG are concerned that this assumption can be biased as this is only based on the opinion of one clinical expert (four experts in total participated in the exercise). The EAG are also concerned about the assumed uncertainty underpinning the HR estimate in the PSA. The standard error is assumed to be 20% of its mean without further justification.

- Modelling the effect of leniolisib on survival using manifestation-specific morality risk

The company conducted a scenario analysis (Doc B, p.185-186) in which mortality under current clinical management was calculated through manifestation-specific mortality risks

rather than an overall mortality risk informed by a case series data of people with APDS. The mortality risks associated with each manifestation were obtained from a retrospective analysis study using CVID patients.[44] Table 24 presents the HRs of mortality for each manifestation.

Table 24: HRs of mortality for each manifestation

Manifestations	HR[a]	Source
Lymphoproliferation	1.67	Odnoletkova et al. (2018)[44]
Gastrointestinal manifestations	0.97	
Lymphoma	5.48	
Cytopenia	1.08	
Bronchiectasis	0.83	
Advanced lung disease[b]	4.85	
Infections	1	Assumption
Hearing loss	1	Assumption

Footnotes: [a]HRs represent a comparison of mortality risks with and without the manifestation within the CVID cohort e.g., mortality risk for CVID patients with lymphoma compared to CVID patients without lymphoma.
[b]Reported for granulomatous lymphocytic interstitial lung disease (GLILD).
Abbreviations: HR: hazard ratio.

A calibration factor was applied to ensure the predicted outcomes were in line with observed overall mortality in APDS patients, yet little information was provided on how this calibration value (i.e., [redacted]) was determined.[14] The EAG requested the company to provide full details on the calculation process of this calibration value. In the PfC, the company mentioned that "the calibration factor was a simple static multiplier of the hazard of mortality".[26] They stressed that the calibration was supported by HTA experts.[26] The company also included visualised results of the survival curve when calibration was not implemented, and results of sensitivity analysis in which the calibration value varies from [redacted]. Based on these results, the company justified that the survival curve with a calibration value of [redacted] provides the best visual fit to the observed overall mortality in APDS patients. In general, the EAG agrees with the company's alternative approach of calculating mortality rate employed in the scenario analysis.

5.2.4.3 Impact of leniolisib treatment on manifestations

- Small sample size in the expert elicitation exercise

In the CS's base case analysis, HRs for the impact of leniolisib on the incidence, and proportions of severity reduction and resolution of manifestations were based on a variety of evidence sources, including: the leniolisib clinical trial programmes (Study 2201 Part II, 2201E1 and EAP survey[22 25 31]) and the modified SEE (Exercise 1 of the Expert Consultancy[39]) as outlined in Table 41, Section B.3.3.4 of the company submission.[14] Evidence from the leniolisib clinical trials was given the highest priority, followed by the EAP data, with the modified SEE data used to address any subsequent gaps.[26]

Five clinicians participated in the modified SEE exercise which was used to generate HR estimates, reduction in severity and resolution of manifestations. They were asked to provide their estimates for the upper and lower plausible limits of manifestation occurrence under leniolisib treatment, and the midpoints of their estimates were used in the primary analysis. The EAG is concerned that the estimates elicited from the survey can be subject to a high level of uncertainty given only 5 clinicians participated in the survey.

- The inconsistent use of evidence across groups with different data quality

The EAG also noticed the inconsistency of using evidence informing the HRs for the impact of leniolisib. Although the criteria for the hierarchical use of clinical evidence were set in Table 41 of the CS Section B.3.3.4, the company did not strictly follow these criteria. The company sometimes used clinical opinions when higher quality of evidence was available (e.g., the HR for Cytopenia and for hearing loss). However, the case of HR for hearing loss seems to be special, as the EAG agrees that in the absence of sufficiently reported incidence in the trials and EAP survey, the use of expert opinion may be more appropriate. In addition, the HR value elicited from clinical experts leads to a more conservative estimation of the benefits associated with leniolisib.

5.2.5 Adverse events

Table 25: Summary of EAG's critique on the adverse events within the economic model

Aspect of model	Section in CS where methods are reported	EAG's assessment
Adverse events used within the model		**Some concerns** No comparisons on AE/TEAEs between leniolisib treatment and standard care. See section 5.2.5.1 for further details.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group		

5.2.5.1 Adverse events used within the model

The company did not incorporate adverse effects into the CEM, as most of the AE/TEAEs reported in the trials were Grade 1 or Grade 2 and therefore assumed to have limited impact on HRQoL. The EAG acknowledge that the incidence of reported AE/TEAEs in the studies conducted by the company (see Table 36, CS Doc B) is similar in the leniolisib and placebo groups. However, the EAG notes that participants in the control (placebo) group were required to refrain from using medications (such as mTOR inhibitors, rituximab and cyclophosphamide therapies) commonly used to manage immune dysregulation in this population. Therefore, treatment outcomes in the placebo group may differ from those patients under current clinical management.

The EAG note that there is substantial uncertainty regarding differences in the incidence of AE/TEAEs between the leniolisib and current clinical management arm. The company did not explore alternative assumptions regarding AEs in the model.

5.2.6 Health-related quality of life

5.2.6.1 Searches for health-related quality of life SLR

The company conducted separate searches for the HRQoL SLR. A reasonable range of databases were searched: Embase, MEDLINE, The Cochrane library databases (CENTRAL and Database of Systematic Reviews), CRD Database (DARE, NHS EED and HTA Database), EconLit and ScHARRHUD database. The searches were run from database inception to date of search. The company run the first systematic search on 11th of November 2021, a subsequent update on 18th May 2023 and a targeted update on 23rd April 2024. Some databases were not included in the last targeted update. The company provides justification for not searching some databases which are reasonable, however a rationale for not searching Econlit has not been provided. For the EAG's evaluation of grey literature

sources and conference sources see Section 4.1.1.1. The EAG's critique of the way past subject headings were not included in all searches (clinical effectiveness, economic, and health-related quality of life) can be found in Section 4.1.1.2. The company restricted searches to HRQoL studies using a filter for health utilities/quality of life. The EAG requested further clarification on the providence of the filter in the PfC letter (B.6 pg. 9). The company response provided in-depth clarification on how the filter was developed and the reasons for broadening existing validated and published filters.[26]

Overall, the EAG are satisfied that the search for HRQoL studies was conducted appropriately.

Table 26: Summary of EAG's critique on HRQoL

Aspect of model	Section in CS where methods are reported	EAG's assessment
Identification of HRQoL data within the SLR	Appendix H1.1, p.182-192	**Some concerns** An appropriate range of databases were used, though one relevant database was omitted in the 2024 targeted update, which may have reduced the amount of eligible HRQoL studies identified by the searches. See Section 5.2.6.1 for further details.
Source of preference data for valuation of changes in health-related quality of life	Document B.3.4.1, p.153-154; Document B. 3.4.3, p.155 & Pharming_Exercise 2_EQ-5D-5L HCP Valuation_20Mar2024 [45]	**Some concerns** Based on NICE HTA guidelines, EQ-5D data directly elicited from the patients is recommended to be used in the model.[1] However, SF-36 instead of EQ-5D values were elicited in the trial studies supporting the CS.[22] [8] [25] **Some concerns** Proxy respondents were used to elicit baseline utility value used in the economic model, which can potentially cause bias. See section 5.2.6.2 for further details.
HRQoL evidence used for the cost effectiveness model	Document B.3.4.5, p.162; p.157-161; Document B.3.4.5, p.162 Document B.3.4.5, p.157-161	**Some concerns** EQ-5D measures were not always used in the elicitation of disutility values for the proxy conditions. **Key issue [4]** Insufficient justification for the additional utility gain due to the emotional benefit of leniolisib. **Some concerns** Inconsistent use of source of age-adjusted utility for the general population (Ara&Brazier 2011[46] or Kind et al. 1999[47] for the denominator of manifestation disutility). See section 5.2.6.3 for further details.
The approach of utility calculation		**Some concerns** The additive approach the company used to calculate the overall disutility from the manifestations can be biased.

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; SLR = systematic literature review

5.2.6.2 *Source of preference data for valuation of changes in health-related quality of life*

- No available EQ-5D data elicited directly from the trials

It is expected that EQ-5D data elicited directly from the patients representing the UK APDS population was used in the model based on the NICE reference guidelines.[1] However, SF-36 rather than EQ-5D was measured in the leniolisib clinical trials to evaluate participant HRQoL.[22 8 25] A brief explanation is given as to why SF-36 was initially chosen as the preference measure in the design stage of the trials. However, the company claimed that SF-36 data from the clinical trials could not be used to inform HRQoL in the base case model because (a) SF-36 could not capture the specific HRQoL benefits important for people living with APDS and lacked sensitivity in detecting meaningful changes in certain domains; (b) baseline SF-36 data from the trials have already included the impact of several manifestations of APDS, and therefore would overestimate the impact of APDS. The company conducted a scenario analysis (scenario 7) in which baseline utility was informed by EQ-5D-3L mapped from the SF-36 data.

The company instead used utility values for proxy conditions obtained from various sources (see Table 27). The EAG believes that SF-36 utility estimates derived from the trial may be most applicable to the model population with external validity issues associated with the alternative estimates from other sources. However, the EAG acknowledge that using mapped values from the SF-36 data may not be ideal for this patient groups and no other studies measuring HRQoL directly from APDS patients have been identified.

The EAG have explored the alternative source of utility for each manifestation using values elicited from the clinicians' EQ-5D exercise in the scenario analysis. In a related assumption in the CS' base case analysis, it was assumed that for patients experiencing improvement in severity of manifestations due to leniolisib treatment, the utility decrement due to those manifestations would be reduced by 50%, based on expert opinion. The EAG have conducted a scenario analysis assuming a 25% reduction.

- Using proxy respondents to elicit baseline utility value used in the economic model

The company stated that baseline utility (i.e., [redacted]) was informed by the clinician EQ-5D vignette study in which clinicians were asked to rate a number of health states according to the dimensions of the EQ-5D-5L by assigning the level they perceive is most accurate to represent the patient's HRQoL in their opinion. The EAG is concerned about the utility estimates elicited from proxy respondents, as there is evidence suggesting that proxy participants tend to overestimate impairment and underestimate HRQoL caused by diseases.[48] For this reason, the EAG conducted scenario analyses using either the baseline utility value informed by data from Study 2201 Part II, or the general population utility value calculated by Ara & Brazier (2010).[46]

Summary results of the clinician EQ-5D vignette study was provided, but the EAG initially identified a value different to that used by the company when using the results to produce an EQ-5D estimate a (i.e., [redacted]; sourced from Vignette G, table 5 of the vignette survey report [45]) in the verification process. The company clarified that this utility of [redacted] used in the model was calculated based on the mean APDS general utility values for males and females after mapping to EQ-5D-3L. The EAG encourages the company to improve their presentation and transparency of the results reported in the EQ-5D vignette study.

5.2.6.3 *HRQoL evidence used for cost effectiveness model*

- EQ-5D based utilities with UK value set were not always used for the proxy conditions

Given the lack of utility data identified from the clinical trials and HRQoL/utility SLR, the company conducted a targeted search to identify utility values associated with APDS manifestations and treatments from proxy conditions. The company also used EQ-5D

surveys completed by the clinicians to derive utility values for the CEM. The utility values, HRQoL methods and proxy conditions for each manifestation were presented in Table 27.

The company aims to include studies using EQ-5D to estimate utility values as much as possible aligning to the NICE guidelines,[1] but acknowledged that "this was not always possible, forming a limitation of the approach." (Section 3.4.5, Doc B, p168[14]) The EAG notices that EQ-5D methods were not used in the calculation of utility multipliers for some manifestations (i.e., Gastrointestinal disorder infection and hearing loss), and non-UK value set was used in the calculation of Cytopenia utility multiplier. In general, the EAG acknowledge the company's attempt in the identification of HRQoL evidence for APDS and accepts the lack of evidence for this rare disease, yet at the same time concerned that these limitations pose challenges to the validity and relevance of the utility values used in the model.

- The assumption of the utility gain from emotional benefit of leniolisib

The EAG understand leniolisib may provide positive impacts on patients' emotional state, therefore affecting HRQoL in addition to the effect captured by the conventional EQ-5D measures. However, no evidence is provided to justify the quantification of this impact in the CS.

The EAG requested the company to provide justification of this utility gain and asked them to conduct a scenario analysis with varying levels of this additional utility gain. In the responses to EAG's request, the company listed three studies in which positive psychological impact, such as positive view of life, optimism and absence of anxiety on HRQoL (measured by EQ-5D), are quantified with results suggesting a utility gain of 0.11-0.17. However, the EAG is still concerned about the validity of this assumption because: (a) the EAG are unsure whether the three observational studies used to justify the assumption of utility gain were identified using a systematic search.[49 50 51 52] It is unclear whether there is evidence of other relevant studies to inform this assumption; (b) the studies identified by the company are based on different cohorts of patients (patients with different conditions in different countries) and therefore the generalisability of the results to APDS patients is uncertain; (c) one of the studies[49] is based on unvalidated study-specific questionnaires, which can lead to biased estimates of the impact of utility gain; (d) perhaps most importantly, as the EQ-5D questionnaire contains a dimension measuring anxiety and depression, there may a double-counting issue if the psychological impact of leniolisib is included in addition to the utility captured by conventional EQ-5D measures.

Regarding the uncertainty of the utility gain in the economic model, the company initially assumed that there was no uncertainty for this utility gain in the PSA. In the PfC, the company conducted a OWSA using a range of 0.08 to 0.12, and a scenario analysis of PSA assuming a 10% standard error around the mean estimate of the utility gain.[26] The company suggested that the results of these additional analyses remain relatively unchanged compared to the initial results in the CS. However, the EAG are concerned that the assumption of 10% standard error is not justified (see Key Issue 2, modelling uncertainty).

Overall, the EAG believe that the evidence used to justify the utility gain due to the psychological impact of leniolisib is highly uncertain and likely to bias CE results. Therefore, the EAG has removed this assumption from the EAG base-case analysis.

- Inconsistent use of source of age-adjusted utility

The company calculated the utility multiplier as the utility for each proxy condition divided by the utility for the UK general population with the same age as the cohort used for the proxy condition. This utility multiplier was then used to calculate the disutility for each manifestation. The EAG note that the age-specific utility for the UK general public used by

the company for the calculation of the utility multiplier for the manifestations was based on the method developed by Kind et al. (1999). [47] In contrast, the company used Ara and Brazier's (2011) method[46] to generate the age-dependent utility decrements. These utility decrements were then used to generate the age-dependent baseline utility applied to the model . The company did not provide justification on the inconsistent use of the methods applied, although the EAG note that this does not have a considerable impact on the CE results.

Table 27: Utility data for proxy conditions used in the economic model

Input description		Utility, disutility or multiplier	Source condition	HRQoL methods
APDS baseline utility (no modelled manifestations or treatments)		[redacted]	APDS	EQ-5D-5L completed by clinicians; Mapped to EQ-5D-3L index scores [5]
Splenomegaly utility multiplier		0.91	Myelofibrosis	EQ-5D-3L (UK value set: Dolan et al., 1997)[53]
Gastrointestinal disorder utility multiplier		0.46	Inflammatory bowel disease (IBD)	Methods unclear (likely a disease-specific measure completed by patients, mapped to EQ-5D, and valued using UK value set by Dolan et al, 1997)[53]
Cytopenia utility multiplier		0.88	Immune thrombocytopenic purpura (ITP)	EQ-5D completed by patients; US value set: Shaw et al. (2005)[54]
Malignancy disutility (first year only)		-0.48	APDS	EQ-5D-5L completed by clinicians; Mapped to EQ-5D-3L index scores (Hernandez Alava et al. (2020)[5]
Malignancy utility multiplier (first year and beyond)		0.86	Diffuse large B-cell lymphoma	EQ-5D-3L completed by patients; UK value set: Dolan et al. (1997)[53]
Infections	**Moderate lower respiratory infection**	-0.003	Not disease-specific	Disability weights based on a global survey (including European countries) that used pairwise comparison methods

	s disutility			in which respondents were asked to indicate which of two health states briefly described to them they considered to be "healthier"
	Severe lower respiratory infections disutility	-0.009		
	Moderate upper respiratory infections disutility	-0.003		
	Herpes zoster disutility	-0.004		
	Infections: weighted average disutility	-0.004		
Bronchiectasis utility multiplier		0.91	Bronchiectasis	EQ-5D-3L completed by patients; UK value set: Dolan et al. (1997)[53]
Advanced lung disease utility multiplier		0.65	Cystic fibrosis	EQ-5D completed by patients; UK value set: MVH group
Hearing loss	**Mild hearing loss disutility**	-0.01	Not disease-specific	Disability weights
	Moderate hearing loss disutility	-0.027		
	Weighted average	-0.02		

Source: CS Doc B, Section 3.4.5 [14]

Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group

5.2.6.4 The approach of utility calculation

The company stated that "starting from the baseline utility, an additive approach was assumed in order to combine the utility impacts of manifestations and treatments when more than one manifestation/treatment is experienced".[14] The EAG thinks that this approach can overestimate the combined effect of disutility when people with APDS experience multiple manifestations. The disutility for people experiencing multiple manifestations can be lower than the aggregated disutilities for each individual manifestations if several similar manifestations affect the same dimension of QoL elicited in EQ-5D questionnaire. The company assumed no lower limit on utility value per cycle. The EAG has explored an alternative assumption in their sensitivity analysis by using a lower limit elicited from the Pharming TTO study. These lower limit value was provided by the company.[6]

5.2.7 Resources and costs

Table 28 summarises the EAG's critique on resources and costs within the economic model.

Table 28: Summary of EAG's critique on resources and costs

Aspect of model	Section in CS where methods are reported	EAG's assessment
Resource use and cost data identified in the SLR	Document B3.1 and Appendix 1	**Appropriate** The EAG agrees that the 3 studies identified by the company on costs and HCRU in APDS did not provide useful evidence relevant to the decision problem for this evaluation.
Intervention costs (Leniolisib acquisition costs)	Document B.3.5.1 and Appendix 1	**Appropriate** The company included information about the full and patient access scheme (PAS) discounted cost associated with the cost per bottle of 60 tablets of leniolisib 70 mg.
Administration costs	Document B.3.15	**Appropriate** The company stated that no additional costs are associated with the administration of leniolisib, beyond acquisition costs.
Adverse event costs	Document B. 3.3.5	**Appropriate**
Health state costs (Manifestations for both Leniolisib and clinical management)	Document B.3.5.2 and appendix K	**Some concerns.** In the absence of published sources of evidence the resource inputs included in the model by the company were based on results from the quantitative survey of the Expert Consultancy project (Exercise 4). The EAG note that there is uncertainty in the ranges of resource use elicited from the experts and this may have an impact on the true level of healthcare resource use applied to both the leniolisib and the current clinical management group. The EAG were not able to verify a substantial number of the unit costs of leniolisib manifestation-specific treatment and current clinical management applied by the company. See section 5.2.7.1 for further comment.
Health state costs (Monitoring for both Leniolisib and clinical management)	Document B.3.5.2 and appendix K	**Some concerns** In the absence of published sources of evidence the resource inputs included in the model by the company were based on results from the quantitative survey of the Expert Consultancy project (Exercise 4). The EAG note that there is uncertainty in the ranges of resource use associated with the monitoring of APDS elicited from the experts and this may have an impact on the true level of healthcare resource use applied to both the leniolisib and the current clinical management group. See section 5.2.7.1 for further comment

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; SLR = systematic literature review

5.2.7.1 Health state costs (Manifestations and monitoring for both leniolisib and clinical management groups)

The company has provided a detailed list of all the manifestation-specific treatment costs for both leniolisib and current clinical management. The EAG notes the following:

- The EAG were not able to verify a substantial number of the unit costs of leniolisib manifestation-specific treatments and current clinical management applied by the company. The EAG suspect that this could be because the company has used outdated eMIT unit prices. The EAG prioritised eMIT as the preferred source of unit costs whenever possible as per section 4.4 of the NICE health technology evaluations manual.[1] The revised list of unit costs included in the EAG base-case analysis has been included in Appendix 1.
- The EAG believe that where the company has included treatment costs for both patients under 18 years of age and over 19 years of age the correct formula for allocating these age-dependent costs has not been applied to the model. The EAG has corrected this issue (as described in section 7.1.1) to ensure that these costs are correctly applied in the excel economic model.
- The company conducted a thorough elicitation process to estimates impact of leniolisib and current clinical management on resource use associated with the manifestations experienced by APDS patients. The EAG acknowledge the difficulties of these process in the field of rare diseases and note that there is uncertainty and large variation in the values elicited from the experts. The EAG note that this may have an impact on the true level of healthcare resource use applied to both the leniolisib and the current clinical management groups.

6 COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

The company's base-case cost-effectiveness results using the PAS discount are shown in Table 29. The analysis compares the cost effectiveness of patients treated with leniolisib with patients treated with current clinical management for the APDS population. Unweighted (weighted) results suggest that leniolisib increases the health outcomes by 10.46 (15.46) QALYs and increases costs by [redacted] per patient; and being more costly and more effective than the current clinical management pathway (ICER = [redacted] for the unweighted and [redacted] for the weighted).

Table 29: Company base-case cost-effectiveness results (under the PAS discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Unweighted results		Weighted results	
						Incremental QALYs	ICER (£/QALY)	Incremental QALYs	ICER (£/QALY)
leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.46	[redacted]	15.46	[redacted]
Current clinical management	1,587,334	34.81	[redacted]						

Sources: CS Doc B, Section 3.9 [14]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

To explore uncertainty within their cost-effectiveness analysis, the company conducted a PSA over 1,000 iterations using the PAS price for leniolisib. The company reported the following weighted PSA results showing leniolisib is more effective with, incremental QALYs increasing to 11.57, and more costly ([redacted]) compared with current clinical management.

The company also reported the simulated PSA results for the QALY weighted results showing that leniolisib has a [redacted] probability of being cost-effective compared with current clinical management at a £100,000/QALY WTP threshold. The unweighted results reduced the probability of leniolisib being cost-effective compared to current clinical management to [redacted] at a £100,000/QALY WTP threshold. Table 30 and Figure 1 show the probabilistic results reported by the company.

Table 30: Probabilistic base-case results, with QALY weighting (with proposed PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Weighted incremental QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
leniolisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.57	17.10	[redacted]	[redacted]
Current clinical management	1,613,679	34.77	[redacted]						

Source: CS Doc B, Section 3.9 [14]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 1: Scatterplot of probabilistic results

Source: CS Doc B, Section 3.10 [14]

6.2.2 One-way sensitivity analysis

The company also conducted one-way sensitivity analyses (OWSA) by varying a selection of model parameters individually. For parameters where empirically-derived 95% CIs were not available, a SE of 10% of the mean was assumed by the company. Parameters were varied within lower and upper bounds set to 2.5% and 97.5% of their 95% CIs.

The results of the OWSA are presented in Table 31 and Figure 2. The parameters with the greatest influence on the ICER were the rate of gastrointestinal manifestations, the rate of advanced lung disease, and the long-term utility impact of lymphoproliferation and splenomegaly for standard care.

Table 31: OWSA results for leniolisib versus current clinical management (top 10 most sensitive parameters only)

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Age specific manifestation rate of Gastrointestinal manifestations	[redacted]	[redacted]	[redacted]
Age specific manifestation rate of Advanced lung disease	[redacted]	[redacted]	[redacted]
Long term QoL impact of lymphoproliferation + splenomegaly for SoC	[redacted]	[redacted]	[redacted]
Leniolisib costs	[redacted]	[redacted]	[redacted]
Bronchiectasis associated airway disease utility multiplier for leniolisib	[redacted]	[redacted]	[redacted]
Age specific manifestation rate of Cytopenia	[redacted]	[redacted]	[redacted]

HR of Immunoglobulin replacement therapy (IGRT) yr 5+	[redacted]	[redacted]	[redacted]
Age specific manifestation rate of Lymphoproliferation	[redacted]	[redacted]	[redacted]
Bronchiectasis associated airway disease utility multiplier for SoC	[redacted]	[redacted]	[redacted]
Resolution of manifestation for Lymphoproliferation	[redacted]	[redacted]	[redacted]

Source: CS Doc B, Section 3.10 [14]
Abbreviations: CS = company submission; ICER = Incremental Cost-Effectiveness Ratio; HR = Hazard Ratio; OWSA = one-way sensitivity analysis; QoL = Quality of Life; SoC = Standard of Care;

Figure 2: Results of the OWSA

[redacted]

Source: CS Doc B, Section 3.10 [14]
Abbreviations: HR: hazard ratio, ICER: incremental cost-effectiveness ratio, IGRT: immunoglobulin replacement therapy (IRT), SoC: standard of care (current clinical management).

6.2.3 Scenario analysis

Scenario results conducted by the company are summarised in Table 32.

The scenario analyses conducted by the company suggest:

- Using the modified SEE clinician estimates had the highest impact on the ICER. This reduced the cost-effectiveness of leniolisib and increased the ICER by [redacted]%, to [redacted]
- Removal of the age-related utility decrements applied within the base case to reflect a gradual decline in HRQoL with age, as seen in the general population, resulted in the biggest improvement in cost-effectiveness, reducing the ICER to [redacted].

Table 32: Results of deterministic scenario analysis results for the company base-case (with QALY weighting and proposed PAS)

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)

	Base case			[redacted]	10.46	[redacted]
1	Source of overall morality for the current clinical management	Case series identified by an SLR	Manifestation-specific mortality	[redacted]	10.18	[redacted]
2	Source of manifestation rates under current clinical management	the cohort of individuals with APDS in the ESID registry data [36] and trial data (Study 2201 Part II) [22]	modified SEE clinician estimate [39]	[redacted]	10.26	[redacted]
3	Impact of leniolisib on manifestations	Various evidence sources, including: the leniolisib trials (Study 2201 Part II and 2201E1 [22] [25], the lleniolisib EAP,[31] and a modified SEE clinician estimate [39]	modified SEE clinician estimate [39]	[redacted]	8.51	[redacted]
4	Resource use reduction for manifestations with reduced severity	50%	25%	[redacted]	10.46	[redacted]
5	Age-related utility decrements	Yes	No	[redacted]	11.01	[redacted]
6	Source of utility data for manifestations	SLR	clinician EQ-5D vignette study [45]	[redacted]	9.95	[redacted]
7	Source of baseline utility	EQ-5D vignette valuation exercise	Study 2201 Part II [22] (SF-36 mapped to EQ-5D-3L)	[redacted]	10.24	[redacted]

8	Source of baseline utility	EQ-5D vignette valuation exercise	general population estimate by Ara&Brazier (2010) [46]	[redacted]	10.52	[redacted]
9	Utility impact reduction for manifestations with reduced severity	50%	25%	[redacted]	9.97	[redacted]
10	Treatment discontinuation rate	Study 2201, Study 2201E1 and the leniolisib EAP [31]	Clinician estimate [39]	[redacted]	5.14	[redacted]

Source: CS Doc B, Section 3.10 [14]
Abbreviations: AE = adverse event; APDS = Activated PI3K delta syndrome; ESID = European Society for Immunodeficiencies; ICER; = incremental cost-effectiveness ratio; QALY = Quality Adjusted Life Years; SLR = Systematic Literature Review

6.3 Model validation and face validity check

6.3.1 Face validity assessment and technical verification

The model has gone through a technical verification process by two separate and independent health economist experts.

6.3.2 Comparison with external data

No external data was used to validate the outcomes from the model.

7 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the considerations discussed in the preceding sections above, the EAG base-case included several adjustments to the company base-case presented in Section 6. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016).

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

7.1.1 EAG base-case

Adjustments made to derive the EAG base-case (using the CS base-case as starting point) are listed below.

Fixing errors

- The pack cost for leniolisib

Excel file: the company stated that pack cost for leniolisib is [redacted], but this is inconsistent with the information in Table 2, Section B.1.2 in the CS which states that "The anticipated list price of leniolisib is [redacted] per pack of 60 tablets, excluding VAT." The EAG have communicated with NICE and confirmed that the correct price per pack should be [redacted] as per their internal records. Therefore, the value in "Cost" Sheet, Cell J16, changed to [redacted].

- The EAG were not able to verify some of the unit costs submitted by the company. An updated list of the unit costs applied to the economic model has been included in Appendix 1.

- Excel file: some of the costs the company used are for the under-18 only but applied to patients of all ages (e.g., Endoscopy under the Gastrointestinal disorders manifestation), The EAG has modified the formula so that it accurately captured the different unit costs applied for resource use applicable to patients under 18 years old and over 19 years old. The EAG has added 18-over costs for these treatments in the "parameter" sheet, and applied the under-18 and over-19 costs where appropriate in the leniolisib and standard of care model engines.

Fixing violations

As mentioned in Section 5.2.2.4, QALY gain weight should not be applied in the base-case as the decision of whether the submission meets the criteria for the QALY gain weight and the magnitude of the weight to be applied (and consequently what ICER threshold to use) should be made by the NICE committee. Therefore, the EAG has presented the unweighted results in the EAG base-case analysis but present the weighted results in a scenario analysis if the results suggest that a QALY gain weight can be applied. As a result, the EAG have modified the following values in the submitted excel economic model: "Results" Sheet, Cell G23 and J23, were changed from 1.5 to 1 for the base-case analysis.

Matters of judgement

- The assumption of the discount rate applied to both costs and health effects

As detailed in Section 5.2.2.3, The EAG acknowledge the potentially large positive impact of leniolisib on the improvement of QoL and life expectancy of people with APDS, yet also uncertainty in the long term effectiveness of leniolisib remains. Therefore, the EAG applied a 3.5% discount rate for both the costs and health effects in the EAG base-case analysis, and conducted a scenario using a 1.5% discount rate for both the costs and health effects in the EAG's scenario analysis. This means in the Excel file, the value in "Setting" Sheet, Cell K26, was changed from 1.5% to 3.5% for the base-case.

- Treatment discontinuation rate

As discussed in Section 5.2.4.1, the EAG think that the treatment discontinuation rate used in the CS's base case is too low, and thus adopted a higher discontinuation rate of14% (point estimate of expert elicitation exercise).

- The additional utility gain assumed for the psychological impact of leniolisib.

As discussed in Section 5.2.6.3, the EAG believe that the evidence used to justify the utility gain due to the psychological impact of leniolisib is insufficient and associated with a high degree of uncertainty, which may bias the CE results. Therefore, the EAG have removed this assumption from the EAG base-case analysis, which means the value in "Utility" Sheet, Cell F17, changed from 0.1 to 0.

- The assumption of using a 20% of the mean estimates as standard errors for input parameters where no information on uncertainty is available.

Most of the input parameters in the CS have no information on uncertainty and thus the company made a 10% SE assumption on these parameters in the probabilistic analysis. However, the EAG considered the justification for using a 10% SE insufficient, and therefore adopted a 20% SE in the EAG probabilistic analysis, which is more conservative than the one used in the CS (see Section 5.2.3.2 for further discussion).

7.1.2 EAG exploratory scenario analyses

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

EAG scenarios

(1) Assuming the treatment discontinuation rate to be 0%, as opposed to 14% in the EAG base case (see section 5.2.4.1)
(2) Assuming the treatment discontinuation rate to be 10%, as opposed to 14% in the EAG base case (see section 5.2.4.1)
(3) Assuming the treatment discontinuation rate to be 30%, as opposed to 14% in the EAG base case (see section 5.2.4.1)
(4) Assuming a 1.5% discount rate for both the cost and health effects of the model, as opposed to 3.5% in the EAG base case (see section 5.2.2.3)
(5) Assuming a starting age of 18 rather than 15 (see section 5.2.2.1)
(6) Assuming a 10% standard error (same as CS) for input parameters without information on uncertainty (probabilistic analysis only)

Scenarios from the CS

(7) Assuming no age-related utility decrement.
(8) Utility of manifestations: using utility values associated with each manifestation from the clinician EQ-5D exercise (see section 5.2.6.2)
(9) Utility of manifestations: assuming the utility impact reduction for manifestations with reduced severity being 25% (see section 5.2.6.2)
(10) Baseline utility: using the baseline utility value informed by data from Study 2201 Part II. [22] Baseline SF-36 data from Study 2201 Part II were mapped to EQ-5D-3L utilities using the mapping algorithm reported by Brazier & Rowen (2009).[7] This leads to a baseline utility of [redacted] (SE assumed to be [redacted]) (see section 5.2.6.2)
(11) Baseline utility: general population utility values are calculated for each cohort using methods set out by Ara & Brazier (2010)[46]. This leads to a baseline utility of [redacted] (SE: [redacted]) (see section 5.2.6.2)
(12) Utility of manifestations: Using the lower bound of the utility value elicited from the Pharming TTO as the lower limit on utilities for this model (see section 5.2.6.2)

7.1.3 EAG subgroup analyses

No additional subgroup analyses were conducted by the EAG.

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

7.2.1 The EAG base case analysis

Table 33 reports the cost-effectiveness results of updating the company base-case model correcting for errors found by the EAG, correcting violations identified by EAG and the individual impact of the matters of judgement by the EAG to generate the EAG base-case results. Once errors and violations have been corrected in the company's base-case model the unweighted deterministic ICER increases from [redacted] to [redacted]. The unweighted probabilistic ICER resulting from the company's base-case analysis slightly decreases from [redacted] to [redacted]

After fixing errors and correcting violations in the company model the impact of the EAG preferred assumptions applied to the company's model is also detailed in Table 33 and summarised below:

- Applying a 3.5% rather than a 1.5% discount rate for the health effects in the model has the biggest impact on the cost-effectiveness results, increasing the ICER amount by about [redacted] (to [redacted]). Compared with the CS base, QALYs for both the leniolisib and standard of care (SoC) arm decreased as did the difference in QALYs between the two arms.
- The removal of the utility gain associated with the positive psychological impact of initiating leniolisib treatment has the next biggest impact on cost-effectiveness resulting in an ICER of [redacted].
- Applying a larger treatment discontinuation rate (mean value derived from the company's expert opinion exercise) greatly decreases both the cost and QALYs for the leniolisib arm, resulting in a drop in the ICER to [redacted].
- Assuming a 20% rather than a 10% SE for input parameters without information on uncertainty available has little impact on the probabilistic cost-effectiveness results

The undiscounted QALY gain from the preferred EAG base-case analysis is 5.86. As this QALY gain is less than 10, the EAG note that the NICE criteria for the application of a QALY gain weight is not met on this occasion.

Table 33: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – deterministic (with QALY gain weight)					
Leniolisib	[redacted]	[redacted]	[redacted]	15.46 (weighted)	[redacted]
SoC	1,587,334	[redacted]			
CS base-case – probabilistic (with QALY gain weight)					
Leniolisib	[redacted]	[redacted]	[redacted]	17.10 (weighted)	[redacted]
SoC	1,613,679	[redacted]			
CS base-case – deterministic (without QALY gain weight)					
Leniolisib	[redacted]	[redacted]	[redacted]	10.46 (unweighted)	[redacted]
SoC	1,587,334	[redacted]			
CS base-case – probabilistic (without QALY gain weight)					
Leniolisib	[redacted]	[redacted]	[redacted]	11.57 (unweighted)	[redacted]
SoC	1,613,679	[redacted]			
Fixing errors (1-3) – deterministic[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	10.46	[redacted]
SoC	1,547,870	[redacted]			
Fixing errors (1-3) – probabilistic[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	11.49	[redacted]
SoC	1,620,167	[redacted]			
Fixing errors (1-3) + fixing violation + applying a 20% standard error for parameters without information on uncertainty – probabilistic[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	11.02	[redacted]
SoC	[redacted]	[redacted]			
Fixing errors (1-3) + fixing violation + applying a 3.5% discount rate to the health effects[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	7.21	[redacted]
SoC	1,547,870	[redacted]			
Fixing errors (1-3) + fixing violation + applying an alternative treatment discontinuation rate elicited from the expert opinion[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	5.14	[redacted]
SoC	1,547,870	[redacted]			
Fixing errors (1-3) + fixing violation + removing the utility gain assumed for the psychological impact of leniolisib[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	8.94	[redacted]
SoC	1,547,870	[redacted]			
EAG base-case (errors 1-3, violation, and matters of judgment 1-3) – deterministic[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	3.54	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SoC	1,547,870	[redacted]			
EAG base-case (errors 1-3, violation, and matters of judgment 1-3) – probabilistic[a]					
Leniolisib	[redacted]	[redacted]	[redacted]	4.51	[redacted]
SoC	1,646,253	[redacted]			

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SoC = Standard of Care
Footnote: (a) Results without the QALY gain weight, as detailed in the section 7.1.1.

The EAG base-case model produced point estimates with accompanying 95% credible intervals in a probabilistic analysis (with 1,000 replications).The estimated EAG base-case ICER), based on the EAG preferred assumptions highlighted in Section 7.1.1, was [redacted] per QALY gained. Incremental QALYs for leniolisib versus current clinical management were 4.51 (95% CrI: -1.76 to 11.78) and incremental costs were [redacted] The probabilistic EAG base-case analyses suggests that leniolisib has a [redacted] probability of being cost effectiveness at willingness to pay threshold of £100,000 per QALY gained. Therefore, usual care would be favoured in the probabilistic results.

These probabilistic results are shown in the form of a cost-effectiveness plane (Figure 3) and a cost-effectiveness acceptability curve (CEAC) (Figure 4).

Figure 3 Incremental cost-effectiveness plane leniolisib versus current standard of care (EAG base-case)

Source: CS model, EAG's base-case

Abbreviations: GBP = pounds sterling; QALY = quality-adjusted life year

Figure 4 Cost-effectiveness acceptability curve (CEACs) leniolisib versus standard of care (EAG base-case)

Source: CS model, EAG's base-case

Abbreviations: CEAC = cost-effectiveness acceptability curve; CS = company submission; EAG = Evidence Assessment Group; GBP = pounds sterling

7.2.2 The EAG scenario and one-way sensitivity analysis.

Table 34 reports the cost-effectiveness results for the EAG's and CS's scenario analyses. Compared with the EAG's base-case deterministic results. Seven of the scenarios resulted in a lower ICER compared with the EAG base case and six of the scenarios yielded a higher ICER compared with the base case. The scenarios with the largest impact on the cost-effectiveness results assessed by the EAG were:

- Changing the treatment discontinuation rate (SC1 and SC3): Increasing the treatment discontinuation rate from 14% to 30% decreases the incremental cost and decreases the incremental QALYs, resulting in a lower ICER [redacted] vs [redacted]). Decreasing the treatment discontinuation rate from 14% to 0% increases the incremental cost and increases the incremental QALYs, resulting in a higher ICER ([redacted] vs [redacted]).
- Setting the discount rate to 1.5% for both costs and effect (SC4): Decreasing the discount rate increases the incremental cost slightly and increases the incremental QALYs, resulting in a lower ICEDR (£[redacted] vs [redacted]).
- Setting lower limit on utilities (SC12): This assumption decreases the incremental QALYs significantly, resulting in an increased ICER (£[redacted] vs [redacted]).

Table 34: EAG scenario analysis results table

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case (deterministic)	N/A	[redacted]	3.54	[redacted]
	EAG base-case (probabilistic)	N/A	[redacted]	4.51	[redacted]
1	Treatment discontinuation rate = 14%	Treatment discontinuation rate = 0%	[redacted]	9.49	[redacted]
2		Treatment discontinuation rate = 10%	[redacted]	4.04	[redacted]
3		Treatment discontinuation rate = 30%	[redacted]	2.80	[redacted]
4	Discount rate = 3.5% for both costs and health effects	Discount rate =1.5% for both costs and health effects	[redacted]	4.62	[redacted]
5	Starting age = 15	Starting age = 18	[redacted]	3.72	[redacted]
6 [a]	A 20% standard error assumption on parameters without information on uncertainty	A 10% standard error assumption on parameters without information on uncertainty	[redacted]	4.49	[redacted]
7	Assuming age-related utility decrement	Assuming no age-related utility decrement	[redacted]	3.61	[redacted]
8	Using utility values for each manifestation from the literature	Using utility values for each manifestation from the clinician EQ-5D exercise	[redacted]	3.65	[redacted]
9	Assuming the utility impact reduction for manifestations with reduced severity being 50%	Assuming the utility impact reduction for manifestations with reduced severity being 25%	[redacted]	3.40	[redacted]
10	Baseline utility informed by the clinician's estimates	Baseline utility informed by the trial data	[redacted]	3.45	[redacted]
11		Baseline utility informed by	[redacted]	3.79	[redacted]

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		general population utility values by Ara & Brazier (2010) [46].			
12	No lower limit on utilities	Lower limit on utilities elicited from TTO tasks	[redacted]	3.12	[redacted]

Source: EAG outputs
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year; TTO = Time trade-off
Table note: (a) Probabilistic analysis results are reported

The EAG conducted one-way sensitivity analyses (OWSA) by varying a selection of model parameters individually. As mentioned in section 5.2.3.2, The EAG prefers a more conservative value of the SE assumption for sensitivity analysis. Therefore, for parameters where empirical 95% CIs were not available, a SE of 20% of the mean was assumed in the EAG OWSA. Parameters were varied within lower and upper bounds set to 2.5% and 97.5% of their 95% CIs.

The results of the OWSA are presented in Table 35 and Figure 5. The parameters with the greatest influence on the ICER are leniolisib costs, the HR of Immunoglobulin replacement therapy (IGRT) yr 5+ and the age specific manifestation rate of Gastrointestinal manifestations. Nine of the top ten parameters included in Table 35 are the same as those included in the company's own top ten most sensitive parameters (see Table 31). The only difference is that the EAG list now includes the "subsequent years discontinuation rate" parameter as having a big influence on the ICER. This is to be expected as the EAG preferred analysis base-case analysis included a 14% discontinuation rate which is considerably higher than the 3.54% discontinuation rate included by the company in their economic model.

Table 35 - OWSA results for leniolisib versus current clinical management

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Leniolisib costs	[redacted]	[redacted]	[redacted]
HR of Immunoglobulin replacement therapy (IGRT) yr 5+	[redacted]	[redacted]	[redacted]
Age specific manifestation rate of Gastrointestinal manifestations	[redacted]	[redacted]	[redacted]
Long term QoL impact of lymphoproliferation + splenomegaly for SoC	[redacted]	[redacted]	[redacted]
Age specific manifestation rate of Advanced lung disease	[redacted]	[redacted]	[redacted]
Age specific manifestation rate of Cytopenia	[redacted]	[redacted]	[redacted]
Subsequent years discontinuation rate	[redacted]	[redacted]	[redacted]

Age specific manifestation rate of Lymphoproliferation	[redacted]	[redacted]	[redacted]
Bronchiectasis associated airway disease utility multiplier for leniolisib	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders (GI) utility multiplier for SoC	[redacted]	[redacted]	[redacted]
Abbreviations: CS = company submission; ICER = Incremental Cost-Effectiveness Ratio; HR = Hazard Ratio; OWSA = one-way sensitivity analysis; QoL = Quality of Life; SoC = Standard of Care;			

Figure 5 Results of the EAG OWSA

[redacted]

7.3 Overall conclusions of the EAG's cost-effectiveness analysis

The EAG base-case fixed the errors in the pack cost for leniolisib, updated several other unit costs applied to the model, and changed the approach the company calculated the age-dependent costs. The EAG base-case also changed the 1.5% discount rate assumption to 3.5% based on the NICE reference case.[1] Other preferred assumptions incorporates into the EAG base case include using an alternative source for the treatment discontinuation rate and removing the additional utility gain due to psychological effects of leniolisib on quality of life.

The EAG base case (probabilistic) results comparing leniolisib with current clinical management yielded 4.51(95% CrI: -1.76 to 11.78) incremental QALYs [redacted] incremental costs. This resulted in an ICER of [redacted] per QALY gained. The probabilistic EAG base-case analyses suggests that leniolisib has a [redacted] probability of being cost effectiveness at willingness to pay threshold of £100,000 per QALY gained. However, the wide confidence intervals suggest a high degree of uncertainty surrounding costs and effects.

The parameters with the greatest influence on the ICER are leniolisib costs, the HR of Immunoglobulin replacement therapy (IGRT) after Year 5 and the age-specific manifestation rate of Gastrointestinal manifestations were found by the EAG to be the parameters with the largest impact on the cost-effectiveness results in the one-way sensitivity analysis.

Treatment discontinuation has the biggest impact on the cost-effectiveness results. For example, increasing the treatment discontinuation rate from 14% to 30% decreases leniolisib treatment costs, significantly reducing the incremental costs from [redacted] to [redacted] whilst also decreasing the incremental QALYs from 4.51 to 2.80 the incremental QALYs, resulting in an ICER of [redacted].

7.4 Overall conclusions of the EAG's critique

7.4.1 Clinical effectiveness

The SLR to identify all relevant clinical evidence on the safety and efficacy of leniolisib to treat patients with APDS was last updated with a targeted update in April 2024. It identified 30 observational or interventional studies and 88 case studies, and the EAG believes it has captured all related evidence relating to the decision problem.

Study 2201 part I (dose-finding study, n=6) provided no major concerns for the EAG, and concluded that 70mg bid was the appropriate dose for the population under consideration.

Study 2201 Part II (RCT, n=31) appears to have been methodologically sound although some areas, such as concealment of allocation, are at unclear risk of bias. The key issue with the RCT is that the comparator group did not receive established clinical management as understood in the UK and defined in the NICE scope. They received a placebo plus restricted symptomatic management but selected immunosuppressants (which the EAG's clinical experts considered reflect standard care) were prohibited, which may have over-estimated the apparent effectiveness of leniolisib. The small sample size (n=31) is appropriate relative to the estimated number of people living with APDS and the rarity of the condition. Part II reported a statistically significant and clinically meaningful change in surrogate co-primary endpoints used to measure immunophenotype normalisation (increased percentage naïve B cells of total B cells) and reduction in lymphoproliferation (change in size of lesions) respectively.

Study 2201E1 (open-label extension trial, n=37) provided leniolisib to participants from part I and part II, plus two other eligible participants. It is due to complete in 2027 and has released interim results, reporting continuing immunophenotype normalisation to day 252, reduction in serum IgM levels, (post-hoc) reduction in the incidence of infections, decreased fatigue, and improved within-patient quality of life scores. It also reported that leniolisib continued to be well tolerated throughout a median of 154.71 weeks.

To provide further evidence the company carried out an indirect treatment comparison which compared leniolisib patients from the extension trial to a real-world sample of control patients from the ESID Registry, who did not have their treatments prohibited (as in the trial). This reported reductions in infection rate and reduction (improvement) in serum IgM levels.

7.4.2 Cost effectiveness

The EAG considers that the company's deviations from the reference case had a large impact on cost-effectiveness results. This is most evident when the discount rate of 3.5% was applied to both costs and effects as per the NICE reference case.

Lack of long-term efficacy and quality of life data was a concern. The EAG appreciates the company was hampered by the lack of data on long term efficacy and quality of life data and sought alternative sources, including a very thorough expert elicitation exercise, to seek the data needed for the economic model. For example, the company had to rely on proxy conditions to apply their manifestation-related utility and expert opinion as there were no useable HRQoL data that could be directly incorporated into the economic model. This is unsurprising given the rarity of the condition and the small number of patients affected by APDS in the UK. This led to a number of assumptions which incorporated a high degree of

uncertainty into the analyses. The EAG are sympathetic to this approach and recognises that emerging longer-term data will be needed to address this uncertainty.

The most influential cost driver in the EAG analysis was the cost of leniolisib itself. This cost is based upon the confidential PAS cost. All analyses used this cost. The costs for each of the health states in the model related to the care of participants from the age of 15. The EAG had some concerns surrounding resource use. Most of the estimates relating to healthcare resource use were derived via an expert elicitation exercise. The EAG note that the wide variation in the estimates provided by the experts leads to uncertainty surrounding the management and monitoring of APDS for both leniolisib and current clinical management patients. Additionally, the analysis was restricted to the NHS and did not include any resources associated with the use of personal and social care services. This was a concern as the manifestations associated with APDS can severely affect the patient's daily activities such as education and work. The EAG note that APDS patients may therefore need extra support that could potentially be provided by personal and social care services and which may increase the costs associated with the condition.

Whilst the probabilistic EAG base-case analyses suggests that leniolisib has a [redacted] probability of being cost effective at willingness to pay threshold of £100,000 per QALY gained, these results carry a high degree of uncertainty surrounding costs and effects suggesting that more research is needed. The EAG analyses also show that some changes in the assumptions incorporated in the model have a substantial impact on the relative cost-effectiveness of leniolisib.

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Appendix 1: Unit costs used by the EAG in the economic model

Tables 36 to 48 outline the unit costs included in the EAG economic model. Any deviations from the company's submission have been marked with an asterisk (*).

Table 36- Unit costs for gastrointestinal maniffestations EAG base-case

Description	Reference	Remarks	Company's unit cost	EAG Unit cost	EAG Comments
Gastroscopy	NHS Reference Costs FY21-22 FE50A	Wireless Capsule Endoscopy, 19 years and over, outpatient procedure	135.40	135.40	Unit costs checked (Service code 301 Gastroenterology service)
Stomach acid medication	BNF 2023	Omeprazole 20mg/5ml oral suspension 75 ml / Packsize 1. Recommended dosage 20 mg once a day	234.00	234.00	Unit costs checked
Anti-diarrhoeal treatment	BNF 2023	Loperamide 2mg tablets. Pack size 30. Dosage up to 16 mg daily in 2 divided doses (https://bnf.nice.org.uk/drugs/loperamide-hydrochloride/#indications-and-dose)	2.24	0.41*	e-MIT
Endoscopy	NHS Reference Costs FY21-22 FE50A and FE50B Gastroenterology service	Wireless Capsule Endoscopy, 19 years and over, outpatient procedure	1,462.56	£648 for 19 years and over * £1,463 for 18 years and under*	FE50AWireless Capsule Endoscopy, 19 years and over @ £ 686 FE50B Wireless Capsule Endoscopy, 18 years and under @ £1,463 .

Table 37- Unit costs for cytopenia - EAG base-case

Description	Reference	Company unit cost	EAG Unit cost	EAG Comments
Transfusion	TA853 https://www.nice.org.uk/guidance/ta853/evidence/appraisal-consultation-committee-papers-pdf-11312270749, cost inflated to year 2022	195.08	353.00*	EAG Unable to verify cost for Transfusion .Assumed costs cost for SA45A (Injection of Rh Immune Globulin or Other Blood Transfusion) has been included as in TA853 Unit costs checked (Average HRG cost taken). £353.00
Biopsy	NHS Reference Costs FY21-22 SA33Z	752.00	752.00	EAG price check ok. Diagnostic bone marrow extraction
Corticosteroid treatment	BNF 2023	8.96	8.96	

Table 38 Unit costs for infections (EAG base-case)

Drug types	Drug names	Company Unit cost	Units per pack	Unit size	Unit	Reference for unit costs; dose	EAG Unit cost	EAG Comments
Antibiotic	Sulfamethoxazole/Trimethoprim	23.68	100	960	mg	BNF; SmPC; dose required 800/160	23.68	Unit costs checked (BNF) .Not e-MIT pricing available
	Azithromycin	0.54	3	500	mg	eMIT; SmPC	0.52*	Unit cost for 3 tablets of Azithromycin 500 mg is £0.52 on emit national database 2023 . Typo assumed
Antiviral	Acyclovir	1.27	25	200	mg	BNF; SmPC	0.74*	Unit costs checked on e-mit database. £0.74
	Valaciclovir	54.55	42	500	mg	eMIT; SmPC	42.19*	Unit costs checked for 42 tablets is £42.19 on emit national database 2023
Antifungal	Itraconazole	2.50	15	100	mg	eMIT; SmPC	4.27*	Unit costs checked £4.27 on eMIT national database 2023
	Voriconazole (loading)	23.82	28	200	mg	eMIT; SmPC ; No information on duration of treatment for Voriconazole (maintenance), currently using dummy numbers	30.41*	Unit costs checked £30.41 on eMIT national database 2023
	Voriconazole (maintenance)							

Table 39 -Unit costs for prophylaxix (EAG base-case)

Drug types	Drug names	Pack cost (£)	Units per pack	Unit size	Unit	Reference for unit costs; dose	EAG Unit costs	EAG comments
Antibiotic	Sulfamethoxazole/Trimethoprim	23.68	100	960	mg	BNF; WHO (Prophylaxis for HIV); dose required 800/160; No information on duration of treatment, currently using dummy numbers	23.68	Unit costs checked BNF Sulfamethoxazole 800 mg, Trimethoprim 160 mg, No e-MIT pricing available
	Azithromycin	0.54	3	500	mg	emit; Guidance on azithromycin prophylaxis; ToT: 6-12 months	0.52*	Unit cost from e-MIT database is £0.52

Antiviral	Acyclovir	1.27	25	200	mg	BNF; SmPC; No information on duration of treatment, currently using dummy numbers	0.74*	Unit costs checked on e-mit database. £0.74
	Valaciclovir	54.55	42	500	mg	eMIT; SmPC; No information on duration of prophylaxis. SmPC: Prophylaxis therapy to be re-evaluated every 6-12 months.	42.19*	Valaciclovir 500 mg on eMIT is £42.19
Antifungal	Itraconazole	2.50	15	100	mg	eMIT; SmPC; No information on duration of treatment, currently using dummy numbers	4.27*	Itraconazole 500 mg on eMIT is £4.27
	Voriconazole	23.82	28	200	mg	eMIT; SmPC; ToT: No longer than 180 days	30.41*	EAG Unable to verify – Voriconazole 200 mg on eMIT is £30.41

Table 40 - Unit costs for malignancy (EAG base-case)

Description	Costs (£)	Reference	Remarks	EAG Unit cost	EAG Comments
Biopsy	726.51	NHS Reference Costs FY21-22 YJ04Z	Core Needle Biopsy of Axillary Lymph Nodes	726.51	Unit costs checked
PET-CT	927.81	NHS Reference Costs FY21-22 RN03A	Positron Emission Tomography with Computed Tomography (PET-CT) of more than Three Areas, 19 years and over	927.81	Unit costs checked
Chemotherapy	642.19	TA874	R-CHOP based on https://www.kingshealthpartners.org/assets/000/003/343/Pan_London_DLBCL_Guidelines_Jan_2020_original.pdf, https://www.nice.org.uk/guidance/ta874/documents/committee-papers	642.19	Costs checked as per TA874
Radiotherapy	1,489.17	NHS Reference Costs FY21-22 SC42Z	Radiotherapy - Preparation for Total Body Irradiation, https://www.nice.org.uk/guidance/ta649/documents/committee-papers	1,489.17	Costs checked by EAG - OK

Corticosteroid treatment	72.86	BNF 2023, per 100mg price	Prednisolone 500microgram tablets. Pack size 28. (https://bnf.nice.org.uk/drugs/prednisolone/medicinal-forms/#tablet)	72.86	EAG price check OK Prednisolone 500micrograms tablet pack of 28 is £10.20 BNF. This unit costs was applied to the model using the company's own formula to derive the unit price per 100 mg per patient
Inpatient oncology care	205.78	Service code 370		205.40*	Unable to verify costs – not enough information – Applied costs for Service 370 for outpatient oncology care first attendance , non-consultant led is £205.40
Follow up care	1,913.98	NHS Reference Costs FY21-22 SA17G	Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 3+	1,913.98	Unit costs checked

Table 41 - Unit costs for bronchiectasis-associated airway disease (EAG base-case)

Description	Costs (£)	Reference	Remarks	EAG unit Price	EAG Comments
Lung function test	179.23	NHS ref cost FY21-22 DZ52Z	Cost includes Spirometry	179.23	EAG costs checked OK
Bronchoscopies	2,203.66	NHS ref cost FY21-22 DZ69A DZ69B Total	Diagnostic Bronchoscopy, 19 years and over	DZ69B £2,203.66 and DZ69A £1,388 *	Also included costs is for 18 years and under DZ69B. Cost for 19 years and over is £1,388 DZ69A – (error in picking up the cost for 19 years and over fixed in the model)

Mucolytics prescribed for bronchiectasis	49.32	BNF 2023 - Carbocisteine 250mg/5ml oral solution / Packsize 1	Most common carbocisteine. Dosage assumed to be 1500 mg daily. (https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/prescribing-information/mucolytics/)	43.80*	EAG costs checked on e-MIT £7.30 per pack. Applied formula per company submission : £7.30*6 = £43.80
Corticosteroids	70.04	BNF 2023 - Itraconazole 250mg/25ml solution for injection ampoules and diluent / Packsize 1	Itraconazole 250mg/25ml solution for injection ampoules and diluent / Packsize 1. recommended dosage 200mg	59.84*	e-MIT cost used. Applied formula used by company submission to get 200mg dose: £74.81/250*200 = £59.84
Bronchodilator	0.41	BNF 2023 - Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials. Pack size 20.	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials. Pack size 20. Salbutamol 2.5mg required	0.47*	e-MIT cost used. Pack of 20 nebulisers = £9.39. Price applied for one vial as per company submission £9.39/20= 0.47
Bronchiectasis inpatient care	2,421.87	NHS ref cost FY21-22, DZ12C, DZ12D	Bronchiectasis weighted average cost calculated	2,516.39*	EAG check. Weighted average of non elective short and long stays is £2,516.39
Hyperbaric Oxygen Treatment	216.98	NHS ref cost FY21-22 DZ33Z	Hyperbaric Oxygen Treatment	216.98	EAG costs checked OK
Non-invasive ventilation	1,161.36	NHS ref cost FY21-22 DZ37B	Non-Invasive Ventilation Support Assessment, 19 years and over	DZ37B Non-Invasive Ventilation Support Assessment, 18 years and under (1,161.36). The cost for 19 years and over DZ37A is 428*	EAG check. Requires fixing formula in excel model to include both

Table 42 - Unit costs for Costs for advanced lung disease (EAG base-case)

Description	Costs (£)	Reference	Remarks	EAG unit cost	EAG comments
Lung function test	179.23	NHS ref cost FY21-22 DZ52Z	Cost includes Spirometry	179.23	EAG check OK
Bronchoscopies	2,203.66	NHS ref cost FY21-22 DZ69A DZ69B Total	Diagnostic Bronchoscopy, 19 years and over	DZ69B cost for 18 years and under: £2,203.66 under DZ69A cost for 19 years and over: £1,388 .*	Also included costs is for 18 years and under DZ69B. Cost for 19 years and over is £1,388 DZ69A – (error in picking up the cost for 19 years and over fixed in the model)
Mucolytics prescribed for bronchiectasis	49.32	BNF 2023 - Carbocisteine 250mg/5ml oral solution / Packsize 1	Most common carbocisteine. Dosage assumed to be 1500 mg daily. (https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/prescribing-information/mucolytics/)	43.80*	EAG costs checked on e-MIT £7.30 per pack. Applied formula per company submission : £7.30*6 = £43.80
Corticosteroids	70.04	BNF 2023 - Itraconazole 250mg/25ml solution for injection ampoules and diluent / Packsize 1	Itraconazole 250mg/25ml solution for injection ampoules and diluent / Packsize 1. recommended dosage 200mg	59.84*	e-MIT cost used £74.81. Apply company calculation for one 200mg dose: £74.81/250*200=
Bronchodilator	0.41	BNF 2023 - Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials. Pack size 20.	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials. Pack size 20. Salbutamol 2.5mg required	0.47*	e-MIT cost used. Pack of 20 nebulisers = £9.39. Price applied for one vial as per company submission
Bronchiectasis inpatient care	2,775.96	NHS ref cost FY21-22 DZ12C, DZ12D	Bronchiectasis weighted average cost calculated	£2,516.39*	EAG check. Weighte average of non elective short and long stays is £2,516.39
Hyperbaric Oxygen Treatment	216.98	NHS ref cost FY21-22 DZ33Z	Hyperbaric Oxygen Treatment	219.98	EAG price check OK
Non-invasive ventilation support	1,161.36	NHS ref cost FY21-22 DZ37B	Non-Invasive Ventilation Support Assessment, 19 years and over	DZ37B Non-Invasive Ventilation Support Assessment, 18 years and under	EAG check. Requires fixing formula in excel model to include both costs

				(1,161.36). The cost for 19 years and over DZ37A is 428*	

Table 43 - Unit costs for hearing loss (EAG base case)

Description	Costs (£)	Reference	EAG unit cost	EAG Comments
Mild hearing loss due to chronic otitis media	1,273.39	NHS ref cost FY21-22 CB02	£2,854 *	Unable to verify use costs for total HRG £2,854 CB02C Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 0
Moderate hearing loss due to chronic otitis media	1,273.39	NHS ref cost FY21-22 CB02	£2,854 *	Unable to verify use costs for total HRG £2,854 CB02C Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 0

Table 44 - Unit Costs for immunosuppressants (EAG base-case)

Drug types	Drug names	Pack cost (£)	Units per pack	Unit size	Unit	Reference for unit costs; dose	EAG Unit cost	EAG comments
Immunosuppressive drug (IS)	Sirolimus (rapamycin) loading dose	172.98	30	2	mg	BNF, EMA recommendation, Treatment duration from trial 2201 Part 2	172.98	Unit price OK as per NICE price check
	Sirolimus (rapamycin) maintenance dose							
	Rituximab	785.84	1	500	mg	BNF, SmPC (rheumatoid arthritis) two 1000mg doses 2 weeks apart, next course 24 weeks later; Treatment duration from trial 2201 Part 2	785.84	EAG price check OK

	Mycophenolate mofetil	6.68	50	500	mg	eMIT; SmPC; Treatment duration from trial 2201 Part 2	6.55*	e-MIT cost used
	Cyclosporin	18.37	30	25	mg	BNF, Abolhassani 2014; Treatment duration from trial 2201 Part 2	18.37	EAG price check OK

Table 45 - Unit costs for steroids (EAG base-case)

Drug types	Drug names	Pack cost (£)	Units per pack	Unit size	Unit	Reference for unit costs; dose	EAG Unit cost	EAG comment
Steroid	Prednisolone	0.30	28	5	mg	eMIT;BNF	0.41*	e-MIT cost used

Table 46- Unit costs for IRT (EAG base case)

Description	Costs (£)	Unit	Unit size	Reference	Remarks	EAG unit cost	EAG comments
SCIG	80.00	g	1.00	BNF;	Note: Dosing information from trial Part 2; Proportion on SC or IV based on ESID registry	80.00	EAG price check OK
IVIG	700.00	g	10.00			700.00	EAG price check OK

Table 47 -Unit costs for HSCT (EAG base-case)

Description	Costs (£)	Reference	Remarks	EAG unit cost	
Bone marrow harvest	7,191.03	NHS ref cost FY21-22 SA18Z		7,191.03	7,191.03
Bone marrow transplant, allogeneic graft	103,129.69	NHS ref cost FY21-22 , SA20A, SA20B, SA21A, SA21B, SA22A, SA22B,SA23A, SA23B		103,627*	EAG costs checked. Weighted average £103627 (small unavailable values suppressed by

					NHS digital replaced by 1 by the EAG)
Follow up costs (first 2 years)	72,923.27	HST18	Cost inflated to year 2022	£68,570*	EAG check: HST 18: £61,965. Prices inflated to 2022

Table 48 -Unit costs for tonsillectomy (EAG base-case)

Description	Costs (£)	Reference	EAG unit cost	
Cost per tonsillectomy	2,501.18	NHS ref cost FY21-22 CA60C	2,501.18	EAG unit cost checked OK

Highly Specialised Technology Appraisal

Leniolisib for untreated activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over [ID6130]
EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 6th August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Executive Summary – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.2, page 11 • *"Reducing the incidence of manifestations for APDS, which in turn reduces quality of life decrements experienced by patients receiving leniolisb compared to those under current clinical management."*	Please amend as follows: • "Reducing the incidence **and prevalence** of manifestations for APDS, which in turn reduces quality of life decrements experienced by patients receiving **leniolisib** compared to those under current clinical management."	For completeness: the company's economic model tracked the age-specific incidence and prevalence of APDS manifestations and treatment use (as described in Section B.3.2.2 in Document B of the CS).	The EAG has incorporated the suggested amendments in full.
Section 1.2, page 12 • *"Using a 3.5% discount rate to both costs and health effects, as per NICE health technology evaluations (HTE) manual,[1] has a large impact on the ICER."*	Please amend as follows: • "Using a 3.5% discount rate to both costs and health effects, as per NICE health technology evaluations (HTE) manual,[2] has a large impact on the ICER." i.e. please change the reference cited from reference #1 (NICE PMG24) in the reference list to reference #2 (NICE PMG36) in the reference list:	Incorrect reference cited. The 3.5% discount rate is cited in Table 4.1 on page 68 of NICE [PMG36].	Thank you for highlighting this. The EAG has now updated the reference

	• "NICE. NICE health technology evaluations: the manual. Process and methods [PMG36]. Last Update Date: 31 January 2022. London: National Institute for Health and Care Excellence (NICE); 2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation [Accessed 28/05/2024]."		
Section 1.3, Table 2, row 2, page 13 • *"Patients with previous or concurrent use of immunosuppressive medications were excluded from the clinical trials, due to potential increased risk of infections."*	Please amend as follows: • "~~**Patients with previous or concurrent**~~ **Prior** use of **relevant** immunosuppressive medications **(such as mTOR inhibitors, rituximab, glucocorticoids [above 10 or 25 mg prednisone or equivalent per day] and cyclophosphamide)** were ~~**excluded from the clinical trials**~~ **allowed providing appropriate use of protocol-defined washout periods**, due to potential increased risk of infections **in the leniolisib and placebo arms**."	To provide clarity and accurate interpretation that only some, not all, classes of immunosuppressive medications were prohibited within the leniolisib clinical trials. Furthermore, patients treated with select classes of immunosuppressive medications could enrol in the study subject to completing a protocol-defined washout period. For example, for mTOR inhibitors, there must not have been use within 6 weeks prior to first study dose, or 4 weeks if the use was short-term (up to 5 days); 23% of participants had prior mTOR inhibitor use at enrolment in Study 2201 Part II. The company	Thank you for your comments. We have revised the wording to clarify eligibility criteria, specify that certain immunosuppressive medications were prohibited, and to emphasise the EAG's main critique that the comparator arm was not representative of established clinical management. See text below: - *"Patients with previous with prior use of certain immunosuppressive*

		have suggested the following amendments to avoid misleading readers that all patients with APDS with previous use of any immunosuppressive medication were ineligible for the clinical trials.	*medications were required to complete a protocol-defined washout period to be eligible for enrolment. More importantly, concurrent use of certain immunosuppressive medications was excluded from the clinical trials, due to potential increased risk of infections"*
Section 1.3, Table 4, row 2, page 15 • *"A review of previous NICE technology appraisals found that most models typically assumed SEs between 10-30% of the mean (20% was most common) for such parameters."*	Please amend by adding the following reference at the end of this statement (reference #38 in the current reference list): • "Lanitis T, Muszbek N, Tichy E. The Probability of a Successful Probabilistic Sensitivity Analysis London: Evidera; 2014. Available from: https://www.evidera.com/wp-content/uploads/2015/04/The-Probability-of-a-Successful-Probabilistic-Sensitivity-Analysis.pdf [Accessed 10th July 2024]."	The proposed reference aligns with the one cited in Section 5.2.3.2 on page 75 of this report: • "The company cited one of the findings of this review that "The variation for the parameters was in most cases assumed and not informed by data, with 68% of TAs including at least one parameter where the standard error was assumed to be 10–30% of the mean, with 20% being	The EAG accept the change and have added the reference mentioned by the company to the end of the statement.

		the most common assumption."	
Section 1.3, Table 5, row 2, page 16 • *"The EAG note that there is no evidence that the efficacy of leniolisib will continue beyond 6 years."*	Please amend as follows: • "The EAG note that there is no **published** evidence that the efficacy of leniolisib will continue beyond 6 years, **although participants from Study 2201 Part I remain on therapy with up to 8 years of follow-up**."	To avoid misinterpretation of the clinical evidence base: although longer follow-up data are available as participants with 6 years of treatment in Study 2201 have subsequently received commercial supply in the US or continued access via the company's Early Access Programme (EAP), these data have not yet been published. For the two European participants from Study 2201 in the EAP, leniolisib treatment has been ongoing for 7.3 to 8.1 years (as of 2nd Aug 2024).[1]	The EAG acknowledge the potential that more evidence from the ongoing clinical trial may change conclusions yet are unable to verify the unpublished evidence mentioned by the company since these data were not submitted by the company. Therefore only a partial amendment was made. The revised text is as below: "The EAG note that there is no **published** evidence that the efficacy of leniolisib will continue beyond 6 years."
Section 1.3, Table 5, row 3, page 16 • *"The EAG propose that the mean discontinuation rate derived from the company's own UK*	Please amend as follows: • "The EAG propose that the mean discontinuation rate derived from the company's own **Expert Consultancy project** is applied to the base-case analysis."	For consistency with the CS and enhanced clarity for readers.	The EAG have incorporated the suggested amendment in full

expert Epic survey is applied to the base-case analysis."			
Section 1.4, Table 7, rows 4, 7 and 10, page 17	Within the "Incremental costs" and "Incremental QALYs" columns, please move the values from the "SoC" rows to the "Leniolisib" rows.	Typographical error: the values are the incremental costs and QALYs associated with leniolisib, as compared with SoC.	Thank you for highlighting this. The EAG have incorporated the suggested amendments in full

Issue 2 Plain Language Summary – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2, page 19 • *"This leads to frequent infections, lung disease (bronchiectasis), inflammatory bowel disease and, in severe cases, malignancies such as lymphomas."*	Please amend as follows: • "This leads to frequent infections, lung disease (bronchiectasis), inflammatory bowel disease and~~, in severe cases,~~ **increased risk of** malignancies such as lymphomas."	Factual inaccuracy: individuals with APDS can still experience severe, progressive and life-threatening multi-system manifestations without malignancy. In various published studies (Maccari et al., 2023, Büsch et al., 2023, Jamee et al., 2019, Coulter et al., 2017), it has been observed that non-malignant causes of early mortality in APDS include severe respiratory infections,	The EAG have incorporated the suggested amendments in full

		bronchiectasis, respiratory failure and cardiopulmonary arrest.[2-5]	
Section 2, page 19 • *"The manufacturer conducted an extended trial which is ongoing."*	Please amend as follows: • "The manufacturer conducted an extended **~~trial~~ open-label study** which is ongoing."	To provide clarity that the open-label extension study did not use a randomised design.	Thank you for the feedback. The concise, plain language summary is intended for people with no prior knowledge and is written at a reading level that is accessible to most people in the UK. We think the term 'open-label study' is too technical for this section. Typical definitions of 'trial' is generally inclusive of all intervention designs. Therefore, the EAG considers the term 'trial' more appropriate to use.

Issue 3 Decision Problem Critique – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.1.1, Table 9, row 8, page 20	Please amend as follows:	Based on the latest regulatory discussions with the Medicines and Health	Thank you for providing the EAG with updated information regarding

• *"Adults and adolescents with APDS 12 years of age and older and weighing 45 kg or more."*
• *"This population differs to that specified in the pre-invitation scope with the addition of a weight restriction. The population is in line with the:*
  ○ *participant eligibility criteria for the pivotal leniolisib trials*
  ○ *the anticipated licence wording from the Medicines and Healthcare products Regulatory Agency (MHRA), and*
  ○ *the population anticipated to receive leniolisib in UK clinical practice."*
	• "Adults and adolescents with APDS 12 years of age and older ~~**and weighing 45 kg or more**~~."
	• *"~~**This population differs to that specified in the pre-invitation scope with the addition of a weight restriction.**~~* The population is in line with the:
	  ○ participant eligibility criteria for the pivotal leniolisib trials
	  ○ the anticipated licence wording from the Medicines and Healthcare products Regulatory Agency (MHRA), and
	  ○ the population anticipated to receive leniolisib in UK clinical practice."
		Products Regulatory Agency (MHRA), the anticipated indication is no longer expected to include the weight restriction.[6] Therefore, the company now considers that the relevant population for this evaluation is "Adults and adolescents with APDS 12 years of age and older", with no explicit reference to the weight restriction. However, the SmPC is expected to state in the 'Posology' section that "There is no recommended dosage for patients weighing less than 45 kg",[6] meaning that the population anticipated to receive leniolisib in clinical practice, the eligibility criteria for the leniolisib trials and the anticipated licence wording from the MHRA are still in alignment.	regulatory discussions with MHRA and changes to the anticipated indication. Based on this update and the justification provided we have incorporated the proposed changes in full.

Section 3.1.1, page 24 • *"The eligible population defined in the CS includes adults and adolescents with APDS who are 12 years and older and weigh 45kg or more.[13] This differs from the pre-invitation scope due to the weight restriction which aligns with the eligibility criteria in the clinical trial programme and the anticipated marketing authorisation by the Medicines and Health Products Regulatory Agency (MHRA). However, the EAG highlights a potential issue with generalisability; the British National Formulary states the mean value weight for 12-year old adolescents is 39kg.[2] Therefore, the 45kg weight restriction may exclude otherwise eligible adolescents.*"	Please amend and remove the following statements, as well as align the confidentiality highlighting: • "The eligible population defined in the CS includes adults and adolescents with APDS who are 12 years and older ~~**and weigh 45kg or more**~~.[13] ~~**This differs from the pre-invitation scope due to the weight restriction which aligns with the eligibility criteria in the clinical trial programme and the anticipated marketing authorisation by the Medicines and Health Products Regulatory Agency (MHRA).**~~ The anticipated marketing authorisation for leniolisib by the MHRA is expected to provide a dosing recommendation only for patients weighing 45 kg or more. However, the EAG highlights a potential issue with generalisability; the British National Formulary states the mean value weight for 12-year old adolescents is 39 kg.[2] In the leniolisib clinical trials, as part of the inclusion criteria, participants were required to weigh over 45 kg. Therefore, the anticipated dosing recommendation	As above.	Thank you for providing the EAG with updated information regarding regulatory discussions with MHRA and changes to the anticipated indication. Based on this update and the justification provided above we have accepted the proposed changes in full.

	for patients weighing 45 kg or more ~~**45kg weight restriction**~~ may exclude otherwise eligible adolescents."		
Section 3.1.1, page 24 • *"The company clarified that two ongoing paediatric clinical trials (NCT05438407 and NCT05693129) are evaluating leniolisib at lower doses (10 mg bid).[15,16]"*	Please amend as follows: • "The company clarified that two ongoing paediatric clinical trials (NCT05438407 and NCT05693129) are evaluating leniolisib at lower doses (**20–70** mg bid **for patients aged 6–11 years, and 10–50 mg bid for patients aged 1–6 years, respectively**).[15,16]"	Factual inaccuracy.	The EAG has incorporated the suggested amendments in full.
Section 3.1.1, page 24 • *"The company justified this deviation by stating that 15 is the average age of people with APDS in the ESID registry."*	Please amend as follows: • "The company justified this deviation by stating that 15 is the **median** age of registration for people with APDS in the ESID registry."	Factual inaccuracy arising from an incorrect description in the CS.	The EAG have incorporated the suggested amendment. However, also note that the wording in the submitted version reflected what was written in the CS. Section 3.3.1, Document B of CS: "However, the model was run for a cohort of individuals starting treatment at age 15, which is the **average** age of people with APDS in the Level 1 (mandatory) dataset of the ESID registry (November

			2023 dataset).” This is not consistent with the median age claim provided by the company in the factual accuracy response. Therefore, the EAG think this is due to ambiguous reporting in the CS rather than a factual error.

Issue 4 Clinical Effectiveness – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 4.1.3, page 27 • *“[…] in summary, 30 unique studies of interventional and observational design were included and underwent synthesis; 88 case studies were included, but all did not undergo data extraction or synthesis […]”*	Please amend as follows: • “[…] in summary, 30 unique studies of interventional and observational design were included and underwent synthesis; **88 unique case studies** were included, but all did not undergo data extraction or synthesis […]”	Factual inaccuracy: the SLR identified 89 case studies, comprising of 88 unique case studies (see Figure 1 of the CS Appendices, page 23).	The EAG agrees there were 88 unique case studies and have amended the report accordingly.
Section 4.1.3, page 27 • *“[…] but all did not undergo data extraction or*	Please amend as follows: • “[…] but all did not undergo data extraction or synthesis~~,~~	The company indicated in Section B.2.1 of Document B that 10 studies/case studies reported on	Thank you for clarifying the selection process. Based on

synthesis, and it is unclear how some reports were selected for inclusion in the results section."	~~**and it is unclear how some reports were selected for inclusion in the results section**~~."	leniolisib; it is these publications that were covered throughout Document B in more detail.	this clarification, we have amended the report.
Section 4.1.3, page 27 • *"To avoid erroneously excluding eligible articles during the SLR updates, it would have been more reliable for the second reviewer to check the eligibility of all the excluded records at abstract and full-text stages […]".*	Please amend as follows: • "To avoid erroneously excluding eligible articles during the **targeted update in April 2024**, it would have been more reliable for the second reviewer to check the eligibility of all the excluded records at abstract and full-text stages […]".	As described in Appendix D.1.2, for the clinical SLR and SLR update in May 2023, two independent reviewers checked the eligibility of each title/abstract and full text article. The EAG's critique is therefore only relevant to the targeted update conducted in April 2024.	The EAG has amended two sentences in Section 4.1.3 to improve accuracy: - *"For the original SLR, two reviewers independently conducted screening, with a third reviewer arbitrating when disagreements could not be resolved, rapid methods were used for ~~both~~* ***the targeted*** *update* ***conducted on 9th April****."* - *"To avoid erroneously excluding eligible articles during the* ***targeted update in April 2024"***
Section 4.1.5, Table 11, row 1, pages 29–32 • *"Study 2201 Part E1"*	Please amend as follows: • "Study **2201E1**"	Typographical error.	Thank you for highlighting. The EAG has incorporated the suggested changes.

Section 4.1.5, Table 11, row 12, column 5, page 30 • *"[…], physical examination finding, laboratory test finding or other assessments."*	Please amend as follows: • "[…] physical examination **findings**, laboratory test **findings** or other assessments."	Typographical error.	Thank you for highlighting. The EAG has incorporated the suggested changes.
Section 4.1.5, Table 11, row 23, column 5, page 32 • *"However, for the results reported, measures of variability such as confidence intervals and p values were ~~not~~ provided."*	Please amend as follows: • "**~~However, for the results reported,~~ M**easures of variability such as confidence intervals and p values were **~~not~~** provided **for some outcomes**."	Factual inaccuracy: measures of variability for appropriate results from Study 2201E1 were provided in Section B.2 of Document B. For example, in Section B.2.6.3 of Document B, p values were provided for annualised infection rates in Study 2201E1 and reductions in antibiotic IRT usage.	Thank you for highlighting. The EAG agrees and has amended the sentence to reflect the suggested change.
Section 4.1.5, Table 12, row 20, column 4, page 37 • *"The company have clearly reported post-hoc analysis, relating mostly to the identification of clinically meaningful differences."*	Please amend as follows: • "The company have clearly reported post-hoc **analyses**, relating mostly to the identification of clinically meaningful differences."	To provide clarity that the company provided multiple post-hoc analyses throughout the CS in Section B.2.	Thank you for highlighting. The EAG agrees and has incorporated the suggested changes.
Section 4.2, page 40 • *"The CS includes three clinical studies that*	Please amend as follows: • "The CS includes three clinical studies that examine the	To correct the name of Study 2201E1, and to provide clarity with	Thank you for highlighting. The EAG agrees and has

examine the efficacy and safety of leniolisib for the treatment of APDS: 2201 Part I, a phase 2 open-label dose-finding study; 2201 Part II, a pivotal RCT; and 2201 Part EI, an open-label extension of 2201 Part II."	efficacy and safety of leniolisib for the treatment of APDS: 2201 Part I, a phase 2 open-label dose-finding study; 2201 Part II, a pivotal RCT; and **2201E1**, an **open-label extension of Study 2201 Part I and Part II**."	regards to participant flow within Study 2201.	incorporated the suggested changes.
Section 4.2.1, Table 14, row 10 ('Outcome measures'), page 45 • *"Lymph node sizes, transitional and naïve B cell frequencies were observed and reported."*	Please amend as follows: • "Lymph node sizes, transitional and naïve B cell frequencies **(as a proportion out of total B cells)** were observed and reported."	To provide further clarity that these B cell frequencies are derived as a proportion of total B cells (rather than frequencies or B cell counts).	Thank you for highlighting. The EAG agrees and has incorporated the suggested changes.
Section 4.2.1, Table 14, row 11 ('Results: Efficacy outcomes'), page 45 • *"A reduction in the frequency of elevated transitional B cells (from 38% to 10%) and an increase of naïve B cell frequency (from 32% to 78%) was observed."*	Please amend as follows: • "**As a proportion of total B cells, a** reduction in the frequency of elevated transitional B cells (from 38% to 10%) and an increase of naïve B cell frequency (from 32% to 78%) was observed."	To provide further clarity that these B cell frequencies are derived as a proportion of total B cells.	Thank you for highlighting. The EAG has incorporated the suggested changes.

Section 4.2.1, Table 14, row 12 ('Results: Adverse events'), page 45 • *"The extension trial reported that leniolisib remained well tolerated after a median exposure of 102 weeks."*	Please amend as follows: • "The extension trial reported that leniolisib remained well tolerated **throughout** a median exposure of **154.71** weeks."	Typographical error ("154.71 weeks" aligns with Table 35 of Document B, Section B.2.10, p113)	Thank you for your comment the EAG agrees and has incorporated the suggested amendment in full.
Section 4.2.2, Table 15, row 10 ('Outcome measures'), page 48 • *"The company provided data for 18 endpoints and outcomes related to the following broad categories[…]"*	Please amend as follows: • "The company provided data for **19** endpoints and outcomes related to the following broad categories."	Typographical error ("19" aligns with the number of endpoints presented in Table 2 of the Clarification Questions, pages 7–9).	Thank you for highlighting. The EAG has incorporated the suggested changes.
Section 4.2.2.1, page 49 • *"Sections B.2.3.1 and B.1.4.3 of the CS, along with expert clinical advice to the EAG, confirm that immunosuppressive medication, specifically mTOR inhibitors and rituximab, typically form*	Please amend as follows: • "Sections B.2.3.1 and B.1.4.3 of the CS, along with expert clinical advice to the EAG, confirm that immunosuppressive medication, specifically mTOR inhibitors**, steroids** and rituximab, typically form ~~**current care standards**~~ **established clinical**	(i) As described in Section B.1.4.3 of the CS, steroids also fall into the immunosuppressive class of medication for current clinical management of individuals with APDS. (ii) To provide clarity and consistency with referring to either	The EAG has incorporated the suggested amendments in full.

current care standards for APDS in the UK."	**management** for APDS in the UK."	"standard of care" or "established clinical management."	
Section B.4.2.2.1, page 50 • *"However, previous or concurrent use of immunosuppressive medications including mTOR inhibitors (sirolimus, everolimus), rituximab and cyclophosphamide were key exclusion criteria for all clinical trials, […]. Glucocorticoids above 10mg or 25mg prednisone or equivalent per day were also prohibited. The company prohibited the use of immunosuppressives due to evidence suggesting they can lead to an increased risk of infections."*	Please replace with the following: • "**Prior use of relevant** immunosuppressive medications **(such as mTOR inhibitors, rituximab, glucocorticoids [above 10 or 25 mg prednisone or equivalent per day] and cyclophosphamide)** were **allowed providing appropriate use of protocol-defined washout periods,** due to **potential** increased risk of infections **in the leniolisib and placebo arms**."	To provide clarity and accurate interpretation that only some, not all, classes of immunosuppressive medications were prohibited within the leniolisib clinical trials. Furthermore, patients treated with select classes of immunosuppressive medications could enrol in the study subject to completing a protocol-defined washout period. For example, for mTOR inhibitors, there must not have been use within 6 weeks prior to first study dose, or 4 weeks if the use was short-term (up to 5 days); 23% of participants had prior mTOR inhibitor use at enrolment in Study 2201 Part II. The company have suggested the following amendments to avoid misleading readers that all patients with APDS with previous use of any immunosuppressive medication were ineligible for the clinical trials.	Thank you for requesting clarity regarding prior use of relevant immunosuppressive medications. The EAG has re-written this section to avoid giving the impression that all patients with APDS who have prior use of any immunosuppressive medication were ineligible. See text below: - *"Previous use of certain immunosuppressive medications was prohibited in the clinical trial programme if administered within a certain timeframe prior to the first dosing of leniolisib or placebo. To be eligible for enrolment participants who had previously used certain immunosuppressive medications were*

			required to complete a protocol-defined washout period (see Table 16 for prohibited medications and corresponding washout criteria). More importantly, concurrent use of some classes of immunosuppressive medications including mTOR inhibitors (sirolimus, everolimus) and rituximab, which form current clinical management, was prohibited in both the treatment and control arms of Study 2201 Part II. Table 16 provides a non-exhaustive list of immunosuppressive treatments that were prohibited throughout Study 2201 Part II, along with corresponding washout criteria." The EAG would like to emphasise that our main point for consideration in section

			4.2.2.1 is the impact of prohibiting medications that are part of established clinical management in the control arm.
Section 4.2.2.2, page 51 • *"[…] participants randomised to the control arm were more severely impacted at baseline compared to participants randomised to the treatment arm, potentially overestimating any treatment benefits observed for leniolisib."*	Please amend as follows: • "[…] participants randomised to the control arm were more severely impacted at baseline compared to participants randomised to the treatment arm, potentially **bringing uncertainty into the observed treatment effect of leniolisib**."	The company understands the EAG's line of reasoning, but the wording could be more balanced given the lack of evidence suggesting treatment benefit has been overestimated; less severity in the leniolisib arm could equally have led to underestimation of the observed treatment effect of leniolisib. For example, participants who received placebo in Study 2201 Part II were subsequently treated with leniolisib in Study 2201E1. Among these participants, 100% experienced reduction in index lesion SPD (n=7).[7] The specific mean changes from baseline (CfB) are presented below (although Study 2201E1 data were not previously presented in the CS or at clarification stage, these data have been included here to provide the	Thank you for providing additional data obtained during Study 2201 E1. We would like to highlight the cautious phrasing "*potentially overestimating"* used in the EAG report and affirm we consider this to be a fair and reasonable assessment. That said, considering the additional data provided and acknowledging difficulties in predicting true impact we cautiously agree to amend the wording.

		EAG with reasonable justification for this amendment: Mean CfB for reduction in index lesion SPD from **Study 2201 Part II** (Table 14.2-2.7.1b):[8] • Leniolisib group, Day 85: –720.505 mm^2 • Placebo group, Day 85: +33.262 mm^2 Mean CfB for reduction in index lesion SPD from **Study 2201E1** (Table 14.2-12.1):[9] • Prior leniolisib exposure group, last available study visit: –647.77 mm^2 • Prior placebo exposure group, last available study visit: –1267.38 mm^2 Considering mean CfB in naive B-cells (as a % of total B cells), again 100% of participants with prior placebo exposure experienced an increase in naïve B cells with leniolisib treatment in Study	

		2201E1. (As above, the CfBs from Study 2201E1 were not previously presented in the CS or clarifications): Mean CfB for naïve B cells from **Study 2201 Part II** (Table 14.2-11.1.1b):[8] • Leniolisib group, Day 85: +30.123 • Placebo group, Day 85: +2.187 Mean CfB for naïve B cells from **Study 2201E1** (Table 14.2-12.1):[9] • Prior leniolisib exposure group, last available study visit: +30.417 • Prior placebo exposure group, last available study visit: +44.239 Therefore, the company would suggest the EAG amend this wording to be more balanced.	

Section 4.2.2.3, page 52 • *"Two endpoints used to inform the economic model, cytopenia and antibiotic use, do not appear to be specified explicitly in the final NICE scope."*	Please amend as follows: • *"**One** endpoint used to inform the economic model, **~~cytopenia and~~ antibiotic use, does** not appear to be specified explicitly in the final NICE scope."*	Factual inaccuracy, amended to be in alignment with Section B.3.3.4 of the CS. Cytopenias are included in the NICE final scope under immunophenotype measures. For example, low lymphocyte counts are medically referred to as leukopenia and low neutrophils as neutropenia.	The EAG has incorporated the suggested amendment in full.
Section 4.2.2.4.1, page 52 • *"The company's 2024 analysis examined the link between surrogate biomarkers and patient outcomes […]"*	Please amend as follows: • "The company's **correlation** analysis **in 2024** examined the link between surrogate biomarkers and patient outcomes, […]"	Provide further clarity regarding the analyses noted by the EAG.	The EAG has incorporated the suggested amendment in full.
Section 4.2.2.4.1, page 52 • *"Additionally, a 2022 modified Delphi survey retrospectively identified relevant variables and clinically meaningful differences for naïve B cells and lymphadenopathy."*	Please amend as follows: • "Additionally, a **2023** modified Delphi survey retrospectively identified relevant variables and clinically meaningful differences for naïve B cells and lymphadenopathy."	Typographical error ("2023" aligns with Document B, Section B.2.4.2, page 68).	The EAG has incorporated the suggested amendment in full.

Section 4.2.2.4.1, pages 52–53 • *"Despite some biological plausibility and evidence supporting naïve B cells as an endpoint, evidence of a consistent association remains unclear. For further details, refer to the company's clarification on lymphadenopathy (Question A7).[10]"*	Please amend as follows: • "[…], refer to the company's clarification on lymphadenopathy **and immunophenotype (B cell normalisation)** [Question A7]."[10]	To provide clarity that clarification question A7 describes B cell normalisation in addition to lymphoproliferation.	The EAG has incorporated the suggested amendment in full.
Section 4.2.2.4.3, page 54 • *"Additionally, there was no statistically significant difference in the physical or mental component summary scores CfB between treatment arms at week 12 (n=12)."*	Please amend as follows: • "Additionally, there was no statistically significant difference in the physical or mental component summary scores CfB between treatment arms at week 12 (**n=27**)."	Typographical error ("n=27" aligns with Study 2201 Part II CSR, Section 11.2.3, page 73; see below) "No meaningful change from baseline in SF-36 score was observed in the CDZ173 70 mg bid group (N=19) and placebo (N=8)"	The EAG has incorporated the suggested amendment in full.
Section 4.2.2.4.3, page 54 • "A mean CfB at week 12 for leniolisib was reported as 13.05mm (SD=20.71, n=19) compared to placebo -2.25mm (SD=28.95, n=8;	Please amend as follows: • "A mean CfB at week 12 for leniolisib was reported as 13.05mm (SD=20.71, n=19) compared to placebo -2.25mm (SD=28.95, n=8**~~; P=0.2213~~**); there was no statistically	Typographical error ("p=0.2113" aligns with Document B, Section B.2.6.7, Table 30, page 103) and adjusted to appear after the second clause for enhanced clarity.	The EAG has incorporated the suggested amendment in full.

P=0.2213), there was no statistically significant difference between the treatment groups."	significant difference between the treatment groups **(p=0.2113)**."		
Section 4.2.2.4.3, page 54 • *"For longer-term improvement, the mean CfB at week 208 in 2201 E1 was –25.63mm (SD=26.62, n=10); […]."*	Please amend as follows: • "~~**For**~~ Long-term ~~**improvement**~~, the mean CfB at **W**eek 208 in Study 2201E1 was 25.63 mm **points of improvement** (SD=26.62, n=10)"	To provide clarity and avoid misinterpretation of results from the open-label extension, Study 2201E1. As described in the CSR, PtGA scores were inverted in order to provide a consistent scale with the PGA, where 0 indicates no disease activity or impact to well-being, and 100 indicates maximum disease activity and maximum impact on well-being.	The EAG has incorporated the suggested amendments in full.
Section 4.3, Table 18, row 7 ('Results'), page 57 • *"The company reported that the treatment group experienced a difference in median annualised change in IgM of -1.09 g/L (95% CI: -1.78 to -0.39) compared to the control group (i.e. leniolisib reduced serum IgM more than standard care)."*	Please amend as follows: • "The company reported that the treatment group experienced a difference in median annualised change in IgM of -1.09 g/L (95% CI: -1.78 to -0.39**, p=0.002**) compared to the control group (i.e. leniolisib reduced serum IgM more than standard care)."	To support interpretation of the statistical difference observed for IgM levels in the indirect treatment comparison.	The EAG has incorporated the suggested amendments in full.

Section 4.3.1, page 57 • *"[…] associated pathogenic gene variant in PI3KCδ (APDS1) or PIK3R1 (APDS2) and lymphoproliferation."*	Please amend as follows: • "[…] associated pathogenic gene variant in PIK3C**D** (APDS1) or PIK3R1 (APDS2) and lymphoproliferation."	Typographical error.	The EAG has incorporated the suggested amendment in full.
Section B.4.3.2.1, page 58 • *"Use of mTOR was also not included in the IPTW analyses. Patients on mTOR were excluded from the treatment population but control […]"*	Please amend as follows: • "Use of mTOR was **considered** in the IPTW analyses. **There were no patients on mTOR in the treatment population (as this population consisted of patients from the clinical studies)** but control participants were […]"	Factual inaccuracy.	The EAG has re-written this sentence for clarity: *"Use of mTOR was considered in the IPTW analyses. However, there were no patients on mTOR in the treatment population, which consisted of patients from the clinical studies. In contrast, 37% of control participants were receiving mTOR at baseline, and 44% at follow-up."*
Section 4.4.1, page 59 • *"[…] co-primary surrogate outcomes (specifically, proportion of naïve to normal B cells) predict*	Please amend as follows: • "[…] co-primary surrogate outcomes (specifically, proportion of naïve to **total** B cells) predict long-term	Typographical error.	Thank you for your comment the EAG agrees and has incorporated the suggested amendment.

long-term clinically relevant outcomes […]"	clinically relevant outcomes […]"		
Section 4.4.1, page 59 • *"The EAG has some concerns because the weighting across arms was not successful for the respiratory infections analysis."*	Please amend as follows: • "The EAG has some concerns regarding the magnitude of effect estimates due to some residual imbalance after IPTW."	To provide more clarity on the EAG's concerns, and potentially a more balanced summary. In the respiratory infections analysis base case, despite the modest sample size, all covariates (age [SMD=0.073], IRT use [SMD=0.165], and baseline infection rate [SMD=0.207]) could be considered balanced as they are below a threshold of 0.25.[10] Across the range of sensitivity analyses conducted, the greatest SMD between arms was 0.313 (age at entry in Analysis 13). While we acknowledge some sensitivity analyses compared populations with residual imbalances, we do not believe this affects the conclusion of the base case nor the consistent statistically significant benefit observed with leniolisib across all analyses.	The EAG accepts that criteria for assessing residual baseline imbalances vary. However the EAG note that Tables 110-112 in Appendix N.2.2 of the CS states that an SMD=0.1 indicates imbalance. Therefore the EAG's statement is consistent with these criteria stated in the CS, therefore no change was made to the text.

Issue 5 Cost Effectiveness – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 5.2.1, Table 20, row 8 ('Synthesis of evidence on health effects'), page 69 • *"The company then did a search on proxy conditions without revealing details of the databases, they searched, total number of records retrieved and date the search was performed."*	Please amend as follows: • "The company then did a search on proxy conditions without revealing details of the databases, they searched, total number of records retrieved and date the search was performed; **these details were provided at the clarification stage (Question B6)**."	Amended to highlight these details were later provided during the clarification stage by the company.	The EAG accepts the change and has updated the related text based on the company's suggestion.
Section 5.2.1, Table 20, row 3 ('Measuring	Please amend as follows:	Factual inaccuracy.	The EAG accepts this change, the relevant text in Section 5.2.1, Table 20

and valuing health effects'), page 69 • *"The company applied a QALY weight of 1.5 to the undiscounted Incremental QALYs in the base case analysis."*	• "The company applied a QALY weight of 1.5 to the **discounted** incremental QALYs in the base case analysis."		has been updated to: "The company applied a QALY weight of 1.5 to the discounted incremental QALYs in the base case analysis."
Section 5.2.3, Table 22, row 3 ('Health states/events and transitions'), page 74 • *"Within each alive health state, the manifestation prevalence and treatment utilisation were estimated using a partitioned approach."*	Please amend as follows: • "Within each alive health state, the manifestation **incidence and prevalence** and treatment utilisation were estimated using a partitioned approach."	For completeness: the company's economic model tracked the age-specific incidence and prevalence of APDS manifestations and treatment use (as described in Section B.3.2.2 in Document B).	The EAG accepts this change, the relevant text in Section 5.2.3, Table 22 has been updated to: "Within each alive health state, the manifestation incidence and prevalence and treatment utilisation were estimated using a partitioned approach."

Section 5.2.3.1, page 74 • *"The EAG is concerned that the inclusion of only 1 clinical expert involved may be insufficient to justify whether the model structure reflects the current clinical pathways of APDS management, as it precludes deliberating about any potential disagreements among clinical experts."*	Please remove this statement.	Formal clinical validation of the model was only conducted with 1 clinical expert. However, in the Expert Consultancy (Exercise 3) three UK clinicians were presented with a diagram containing all of the treatments used in the company's economic model, and agreed that the diagram captured the relevant treatments and procedures routinely performed for individuals with APDS in their local region.	The EAG has reviewed the further evidence the company has provided and accepts the changes the company suggested. The EAG has removed the original statement in the EAG report and added a statement reflecting the findings from the structured expert elicitation (Exercise 3). The relevant text has been updated to: "The company mentioned that "the final model structure was chosen to reflect key characteristics of APDS and data availability, and was validated by three HTA experts and one UK clinical expert."[11] **In the Expert Consultancy (Exercise 3), another three UK clinicians were presented with a diagram containing all of the treatments used in the company's economic model, and agreed that the diagram represents their region's treatment patterns for patients with APDS.[12]"** Overall, the EAG have amended their critique accordingly (Section 5.2.3.1)

Section 5.2.4, Table 23, row 3 ('Impact of treatment on mortality'), page 77 • *"The EAG is concerned that, as acknowledged by the company, some clinical experts did not have the prior clinical experience to respond to specific manifestation or treatment questions."*	Please remove this statement, or amend as suggested below:. • "The EAG is concerned that~~, as acknowledged by the company,~~ some clinical experts ~~did not have the prior clinical experience to respond to specific manifestation or treatment questions~~ who participated in Exercise 1 of the Expert Consultancy may have had limited experience treating APDS patients, given the ultra-rarity of the condition worldwide."	The company did not acknowledge that clinical experts did not have the required expertise to respond to questions in Exercise 1 of the Expert Consultancy. Clinical experts were identified to take part in the Expert Consultancy based on their prior experience of treating people with APDS in clinical practice. The included physicians have all treated multiple people with APDS, including the six physicians based in the UK, and are therefore some of the most	The EAG accept this change, the relevant text in Section 5.2.4, Table 23 has been updated to: "The EAG is concerned that some clinical experts who participated in Exercise 1 of the Expert Consultancy may have had limited experience treating APDS patients, given the ultra-rarity of the condition worldwide."

		experienced individuals with regards to APDS management in the UK. Inclusion criteria for Exercise 1, which informed the expected effect of leniolisib on manifestations and mortality in the economic model, required included clinicians to have experience with treating multiple people with APDS, as well as experience with leniolisib treatment in people with APDS. Please refer to page 7 of the Expert Consultancy report (reference #14 in Document B).	

Section 5.2.4.1, page 78 • *The company stated that "With clinical trial data available for up to six years, there is no evidence of treatment waning, so the benefits of leniolisib are expected to be sustained lifelong."*	Please amend this quote as suggested below: • The company stated that "~~**With clinical trial data available for up to six years, there is no evidence of treatment waning, so the benefits of leniolisib are expected to be sustained lifelong**~~. "**Due to the mechanism of action (MoA) of leniolisib (as described in Section B.1.2 of the CS), a treatment waning effect was not expected. Furthermore, no evidence of treatment waning has been observed in the leniolisib clinical trials, with up to six years of published data from Study 2201E1 available**", and continued treatment for up to two years in the EAP (as of 2nd August 2024).[1] **Furthermore, an advisory board that convened with six UK experts, included focused discussion on the implications of the MoA of leniolisib, agreed that based on leniolisib's MoA, they did not foresee any likelihood of treatment response diminishing over time. One clinician also clarified that treatment effect waning in this context would be restricted to biologics (e.g. monoclonal antibodies)."**	Amend quote to the justification presented in Section B.3.2.2 Document B (Table 3), for completeness of the justification provided by the company in the CS (Table 3 and page 128 of Section B.3.2.2, Document B), as well as at the clarification stage (Question B3) and the subsequent Addendum of additional Evidence provided.	The EAG accept this change, the relevant text in Section 5.2.4, Table 23 has been updated to: "The company stated that 'Due to the mechanism of action (MoA) of leniolisib (as described in Section B.1.2 of the CS), a treatment waning effect was not expected. Furthermore, no evidence of treatment waning has been observed in the leniolisib clinical trials, with up to six years of published data from Study 2201E1 available [13]', and continued treatment for up to two years in the EAP [14].' In addition, an advisory board that convened with six UK experts, included focused discussion on the implications of the MoA of leniolisib, agreed that based on leniolisib's MoA, they did not foresee any likelihood of treatment response diminishing over time. One clinician also clarified that treatment effect waning in this context would be restricted to biologics (e.g. monoclonal antibodies)." However, the EAG's critique in Section 5.2.4.1 still holds, as long term evidence is still lacking at this stage and the possibility of the

			treatment waning should still be considered.
Section 5.2.4.1, page 78 • *"Having examined the clinical expert responses to the company's own UK epic survey[…]"*	Please amend as follows: • "Having examined the clinical expert responses **in** the company's own **Expert Consultancy project** […]"	To provide consistency with the CS and enhanced clarity for readers, the company would suggest that "Expert Consultancy" is referred to throughout the EAG report.	The EAG accepts this change and has updated the relevant text on p.78, section 5.2.4.1 to "Having examined the clinical expert responses in the company's own Expert Consultancy project […]"
Section 5.2.4, page 79 "The company conducted a scenario analysis (Doc B, p.196-197) in which mortality […]"	Please amend as follows: "The company conducted a scenario analysis (Doc B, p.**185-186**) in which mortality […]"	Incorrect page reference.	The EAG accepts this change and has corrected the page reference.
Section 5.2.4, page 80	Please amend as follows: • "[…] the observed overall mortality in **APDS** patients."	Typographical error.	The EAG accepts this change and has corrected the typo.

"[…] the observed overall mortality in PADS patients."			
Section 5.2.6, page 84 "There is no explanation as to why SF-36 was initially chosen as the preference measure in the design stage of the trials."	Please amend as follows: • "**A brief** explanation **is given** as to why SF-36 was initially chosen as the preference measure in the design stage of the trials."	A brief justification of the use of SF-36 in the trials is given at the top of Section B.2.6.7 (p.99 of CS), therefore we would like the language in this phrase of the EAG report to be softened accordingly.	The EAG has incorporated this amendment in Section 5.2.6.2, Page 87
Section 5.2.6, page 84 "[…] SF-36 could not capture specific HRQoL benefits of APDS patients and lacked sensitivity in detecting meaningful changes; […]."	Please amend as follows: • "[…] SF-36 could not capture **the specific HRQoL benefits important for people with APDS** and lacked sensitivity in detecting meaningful changes **in certain domains**; […]."	To improve clarity, and because the omission of "in certain domains" may be misleading.	The EAG has incorporated this amendment in Section 5.2.6.2, Page 87
Section 5.2.6, page 84	We believe that the incorrect reference has been used to support this sentence. Reference #38 is Lanitis et al.	Incorrect reference.	The EAG accepts the change and has incorporated the right reference, which

"[…] evidence suggesting that proxy participants tend to overestimate impairment and underestimate HRQoL caused by diseases.[38]"	2014, which is a review on probabilistic sensitivity analysis.		is "**Stacey Rand and James Caiels. Using Proxies to assess Quality of Life: A Review of the Issues and Challenges. QORU. May 2015. Retrieved from: https://www.pssru.ac.uk/pub/4980.pdf** "
Section 5.2.6, Table 27, row 2 ('APDS baseline utility (no modelled manifestations or treatments'), page 86 "EQ-5D-5L completed by clinicians; Mapped to EQ-5D-3L index scores"	Please amend as follows: • "EQ-5D-5L completed by clinicians; Mapped to EQ-5D-3L index scores **(Hernandez Alava et al. (2020)[4]**." i.e. please add reference #4 from the reference list: • "Alava M, Pudney S, Wailoo A. *Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an english population study*. Sheffield: Health Economics and Decision Science, School of Health and Related Research. University of Sheffield; 2020. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/estimating-the-relationship-betweenE-Q-5D-5L-and-EQ-5D-3L.pdf [Accessed 10th July 2024]."	For completeness and to align with the EAG's approach for row 6 in Table 27, page 86.	The EAG has added this reference to Table 27
Section 5.2.7, Table 28, rows 6 and 7 ('Health state costs	Please amend as follows:	Typographical error, as the values	The EAG accepts the changes and corrected the typos accordingly.

(Manifestations for both Leniolisib and clinical management'), page 89 • *"[…] resource use elicited from the expert and this may have an impact on the true level of healthcare resource use […]"* • *"[…] associated with the monitoring of APDS elicited from the expert and this […]"*	• "[…] resource use elicited from the **experts** and this may have an impact on the true level of healthcare resource use […]" • "[…] associated with the monitoring of APDS elicited from the **experts** and this […]"	were elicited from multiple experts.	
Section 5.2.6.4, page 88 • *"These lower limit values were provided*	Please remove this statement.	The "lower limit" feature of the model was a diagnostic feature which was not	As detailed in section 5.2.6.4, the EAG considered the approach used to calculate the combined utility in CS as problematic, and applied a lower limit on utility as an explorative approach to

by the company."		meant to be used for analysis, which is why the CS and Document B did not present lower limit values or analysis results. These should kindly be ignored by the EAG. The lowest utility value elicited in the TTO study corresponded to a health state limited to infections, lymphoproliferation, bronchiectasis, cytopenias, and GI disease, with a mean utility of 0.33 (SE 0.02), and did not capture the impact of lymphoma or other manifestations which would lower this utility further, given the	mitigate the issue of overestimation of the combined utility. The lower limits on utility sourced from clinicians or the TTO tasks were provided by the company in the model file and was set as an option to modify the model in the "Setting" sheet of the model submitted by the company. The EAG appreciates the provision of additional sources on lowest utility values. By reading the justification in the factual accuracy response provided by the company, the EAG understands that the value sourced from clinicians provided in the original model sheet document was only preliminary and the correct lowest value elicited from the Clinician EQ-5D study was -0.109 (SD 0.229), representing a health state including infections, lymphoproliferation, bronchiectasis, autoimmune cytopenias, GI disease, lymphoma, fatigue, hearing loss. Given that this elicited lowest value is lower than the one in the CS base case (i.e., 0.1063, the lowest combined utility in the SoC arm; see column BK in the 'SoC model engine' of the CS model), the EAG believes the scenario analysis using the lowest utility value from

		significant burden of these manifestations on people with APDS, as described in Document B, Section B.2.6.6 of the CS. While the company feels it is inappropriate to set a lower limit on utilities using this value, for transparency, the company's base case weighted ICER using this TTO value is £[redacted] per QALY gained. The EQ-5D utility included in the Excel model submitted to the EAG was incorrectly incorporated as [redacted]; this was only a preliminary value,	clinicians is not a meaningful test (i.e. Scenario 13), and has removed this analysis and results from the EAG report. However, the EAG still thinks that the scenario analysis using the lower limit on utilities elicited from TTO tasks (i.e. Scenario 12) is meaningful and decided to retain this in the EAG analysis.

		which was not corrected during model validation as it was not intended to be part of any submitted analysis. The lowest value elicited from the Clinician EQ-5D study was -0.109 (SD 0.229), representing a health state including infections, lymphoproliferation, bronchiectasis, autoimmune cytopenias, GI disease, lymphoma, fatigue, hearing loss. For transparency, using this value as a lower limit in the company base case results in a weighted ICER of £[redacted].	

Section 5.2.7.1, page 90 "[…] detailed list of all the manifestation-specific treatment or both leniolisib […]"	Please amend as follows: • "[…] detailed list of all the manifestation-specific treatment **costs for** both leniolisib […]"	Typographical error.	Thank you for highlighting this. The EAG have amended the text

Issue 6 Cost Effectiveness Results – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 6.2.1, page 93 "[…] leniolisib being cost-effective compared to usual care to […]"	Please amend as follows: • "[…] leniolisib being cost-effective compared to **current clinical management** to […]"	The amendment aligns the naming of the comparator arm with the rest of the CS and EAG report.	Thank you for highlighting this. The EAG has amended the text
Section 6.2.2, Table 31, row 6 ('Bronchiectasis associated airway disease utility multiplier for leniolisib'), page 95 "[redacted]"	Please amend as follows: "[redacted]"	Typographical error.	Thank you for highlighting this. The EAG has amended the text
Section 6.2.2, Table 31, row 9 ('Age specific manifestation rate of Lymphoproliferation'), page 96	Please amend as follows: "[redacted]"	Typographical error.	Thank you for highlighting this. The EAG has amended the text

“[redacted]”			

Issue 7 Evidence Assessment Group’s Additional Analyses – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 7.2.1, Figure 3, page 105	Please add appropriate confidentiality highlighting to the figure.	Results of economic analyses for leniolisib versus current clinical management are commercially sensitive.	Thank you for highlighting this. The Figure has now been amended and it has been included as image only in line with previous NICE HST submissions to ensure confidentiality
Section 7.2.2, Figure 4, page 106	Please add appropriate confidentiality highlighting to the figure.	Results of economic analyses for leniolisib versus current clinical management are commercially sensitive.	Thank you for highlighting this. The Figure has now been amended and it has been included as image only in line with previous NICE HST submissions to ensure confidentiality
Section 7.2.2, Figure 5, page 109	Please add appropriate confidentiality highlighting to the figure.	Results of economic analyses for leniolisib versus current clinical management are commercially sensitive.	Thank you for highlighting this. The Figure has now been amended and it has been included as image only in line with previous NICE

			HST submissions to ensure confidentiality
Section 7.4.1, page 109 • *"The SLR to identify all relevant clinical evidence on the safety and efficacy of leniolisib to treat patients with APDS was last updated in May 2023."*	Please amend as follows: • "The SLR to identify all relevant clinical evidence on the safety and efficacy of leniolisib to treat patients with APDS was last updated **with a targeted update** in **April 2024**."	Factual inaccuracy: targeted updates were carried out for all evidence streams in April 2024.	Thank you for highlighting this. The EAG have amended the text.
Section 7.4.1, page 110 • *"[…] received a placebo plus restricted symptomatic management but immunosuppressants were prohibited, which […]"*	Please amend as follows: • "[…] received a placebo plus restricted symptomatic management but **selected** immunosuppressants were prohibited, which […]"	To clarify that certain doses of steroids were permitted during the trials.	The text has been amended.
Section 7.4.1, page 110 • *"Study 2201E1 (open-label extension trial, n=38) provided […]"*	Please amend as follows: • *"Study 2201E1 (open-label extension trial, n=**37**) provided […]"*	Factual inaccuracy.	Thank you for pointing this out, this text has been amended.

Section 7.4.1, page 110 • *"[…] reporting continuing immunophenotype normalisation to day 252 (n=**5**), reduction […]"*	Please amend as follows: • "[…] reporting continuing immunophenotype normalisation to Day 252 (n=**24**), reduction […]"	Factual inaccuracy in alignment with the first interim analysis of Study 2201E1.[15]	Thank you for the comment, the text has been amended.
Section 7.4.1, page 110 • *"It also reported that leniolisib continued to be well tolerated for a median of 102 weeks."*	Please amend as follows: • "It also reported that leniolisib continued to be well tolerated **throughout** a median **exposure** of **154.71** weeks."	Typographical error ("154.71 weeks" aligns with Table 35 of Document B, Section B.2.10, p113).	Thank you, the text has been amended.

Issue 8 Appendix 1 – Typographical errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 40, row 6 ('Corticosteroid treatment'), column 5, page 120 • "7.86"	Please amend as follows in both columns 5 and 6: • "7**2**.86"	Typographical error.	Thank you for highlighting this, The typo has now been corrected in column 5. No change to unit price is needed in column 6 as this is the correct unit price as applied by the company in the formula included in their CS economic model

Table 40, row 7 ('Inpatient oncology care'), column 2, page 120 • "Service code 370."	Please amend as follows: • "**NHS ref cost FY21-22, medical oncology service (total outpatient attendance tab),** service code 370, unit cost including both consultant-led and non-consultant led."	For completeness and factual accuracy.	We thank the company for the clarification. This is not a factual inaccuracy as this additional information was not included in the company submission. No change needed
Table 41, row 5 ('Corticosteroids'), columns 5 and 6, page 121 • "59.8**4**"	Please amend as follows in both columns 5 and 6: • "59.8**5**"	We align with the cost checked against e-MIT (£74.81 per dose); however, we would propose that the value should be rounded to 59.8**5** (£74.81/250*200 = 59.848).	No change needed. The EAG consider this to be a matter of judgement with no impact on the cost-effectiveness results
Table 41, row 6 ('Bronchiectasis inpatient care'), column 3, page 121 • "NHS ref cost FY21-22, DZ12C, DZ12D."	Please amend as follows: • "NHS ref cost FY21-22, DZ12C, DZ12D, **DZ12E and DZ12F."**	Factual inaccuracy arising from an incorrect description in the CS.	We thank the company for the clarification. No factual inaccuracy as this additional information was not included in the company submission. We do not think any change is required.
Table 42, row 5 ('Corticosteroids'), column 5, page 122 • "59.8**4**"	Please amend as follows in column 5: • "59.8**5**"	Please see justification in row above.	See response above

Table 42, row 7 ('Bronchiectasis inpatient care'), column 3, page 122 • "NHS ref cost FY21-22 DZ12C, DZ12D"	Please amend as follows: • "**Weighted average of total cost (including elective, non-elective, day and night cases)** from NHS ref cost FY21-22 DZ12C, DZ12D."	For completeness and factual accuracy.	We thank the company for the clarification. This is not a factual inaccuracy as this additional information was not included in the company submission.
Table 43, row 2 ('Mild hearing loss due to chronic otitis media'), column 3, page 123 • "NHS ref cost FY21-22 CB02."	Please amend as follows in column 3: • "**Weighted average of** NHS ref cost FY21-22 CB02 (A, B, C, D, E, F)."	For completeness and factual accuracy.	We thank the company for the clarification. This is not a factual inaccuracy as this additional information was not included in the company submission.
Table 47, row 3 ('Bone marrow transplant, allogeneic graft'), column 2, page 124 • "NHS ref cost FY21-22 , SA20A, SA20B, SA21A, SA21B, SA22A, SA22B,S A23A, SA23B."	Please amend as follows in column 2: • "Weighted average of NHS ref costs FY21-22 , SA20A, SA20B, SA21A, SA21B, SA22A, SA22B,S A23A, SA23B (not replacing the unavailable values)."	For completeness and factual accuracy.	We thank the company for the clarification. This is not a factual inaccuracy as this additional information was not included in the company submission.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Section 1.4, Table 7, row 7, page 17	*"11.49"*	Please remove confidentiality highlighting.	No change required please see note* below.
Section 5.2.3, page 75	*"[…] willingness-to-pay threshold of £100,000/QALY dropped from [redacted] implying a moderate impact of change of scenario on CE results."*	Please amend as follows: "[…] willingness-to-pay threshold of £100,000/QALY dropped from [redacted] implying a moderate impact of change of scenario on CE results."	Thank you for highlighting this. The EAG have amended the text.
Section 5.2.3, page 77	*"[…] at a willingness-to-pay threshold of £100,000/QALY dropped from [redacted] […]"*	Please amend as follows: "[…] at a willingness-to-pay threshold of £100,000/QALY dropped from [redacted] […]"	As above.
Section 5.2.4, page 80	*"[…] little information was provided on how this calibration value (i.e., [redacted]) was determined."*	Please amend as follows: […] …little information was provided on how this calibration value (i.e., [redacted]) was determined."	Thank you for highlighting this. The EAG have amended the text
Section 5.2.4, page 80	*"[…] in which the calibration value varies from [redacted]."*	Please amend as follows: "[…] in which the calibration value varies from [redacted]."	Thank you for highlighting this. The EAG have amended the text

Section 5.2.4, page 80	*"[…] justified that the survival curve with a calibration value of [redacted] provides […]."*	Please amend as follows: "[…] justified that the survival curve with a calibration value of [redacted] provides […]."	Thank you for highlighting this. The EAG have amended the text
Section 5.2.6, page 86 (in Table 27, row 1)	*Utility, disutility or multiplier "[redacted]"*	Please amend as follows: Utility, disutility or multiplier "[redacted]"	Thank you for highlighting this. The EAG have amended the text
Section 6.2.3, page 96	*"[…] increased the ICER by 50%, to [redacted]"*	Please amend as follows: "[…] increased the ICER by 50%, to [redacted]"	No change required please see note* below
Section 7.1.2, page 101	*"This leads to a baseline utility of [redacted] (SE assumed to be [redacted])"*	Please amend as follows: "This leads to a baseline utility of [redacted] (SE assumed to be [redacted])"	Thank you for highlighting this. The EAG have amended the text
Section 7.1.2, page 101	"This leads to a baseline utility of [redacted] (SE assumed to be [redacted])"	Please amend as follows: "This leads to a baseline utility of [redacted] (SE assumed to be [redacted])"	Thank you for highlighting this. The EAG have amended the text
*Note from EAG: Please note that CiC highlight has been applied to all costs and QALYs relating to the technology to preserve confidentiality, ICERs are not marked as CiC in the report. This will ensure a transparent presentation of the cost-effectiveness results in the form of ICERs whilst preserving confidentiality surrounding costs and benefits. This approach is consistent with previous NICE STA and HST submissions			

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3. Katharina Büsch HM, Heather M. McLaughlin, Amanda Harrington,. Mortality in Patients With Activated Phosphoinositide 3 Kinase Delta Syndrome: A Systematic Literature Review. American College of Allergy, Asthma & Immunology (ACAAI) 2023 Annual Scientific Meeting. Anaheim, CA, 2023.
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