National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Genetic Alliance UK	It is unclear as to why this technology has been routed via STA rather than the HST route. Given the small population size, severity of the condition and lack of alternative treatments available, it is likely that this treatment will be disadvantaged going through the STA route. The prevalence of activated phosphoinositide 3-kinase delta syndrome (APDS) stated in the background information is 0.01 in 10,000 people which would equate to an approximate population size of 67 people in the UK (based on a UK population of 67 million). This population size clearly meets the first two criteria for routing via the HST pathway. The severity of the condition and lack of alternative treatments would also qualify this treatment to be routed via the HST pathway	Thank you for your comment. The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a highly specialised technology evaluation.

Section	Stakeholder	Comments [sic]	Action
	Immunodeficiency UK	Agree.	Thank you for your comment.
	Pharming Technologies BV	Pharming consider that it is appropriate for leniolisib to be referred to NICE for appraisal. However, Pharming do not consider it appropriate for leniolisib to be evaluated through the single technology appraisal (STA) route, and instead believe that a highly specialised technology (HST) evaluation would be most appropriate. Pharming are in agreement with NICE, in that leniolisib meets the first and second criteria for routing to the HST evaluation programme: activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) is a very rare condition, and no more than 300 people in England would be eligible for treatment with leniolisib. As per the European Medicines Agency (EMA) orphan designation for leniolisib, APDS is estimated to affect approximately 1 individual per 1,000,000 in the European Union (EU).[1] However, whilst the draft HST criteria checklist produced by NICE for leniolisib states that it is unclear whether leniolisib has met the third and fourth criteria, Pharming are confident in the evidence that supports leniolisib in meeting these criteria. Full details of relevant supportive evidence have been provided in the response from the company to the HST criteria checklist, with an overview of the evidence provided here. **<u>Criterion 3: APDS is a very rare condition that significantly shortens life and severely impairs quality of life</u>** Available studies and reviews have reported early mortality due to complications of APDS, with 40-year survival estimates falling below 60%, including both malignant and non-malignant causes.[2-6] Lymphoma-free survival falls to approximately 22% by age 40, with the median age of onset of lymphoma between 18–24 years (and malignancy reported at as early as	Thank you for your comment. The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a highly specialised technology evaluation. Thank you for you comment. Comment noted.

Section	Stakeholder	Comments [sic]	Action
		18 months of age).[3-6] Malignant lymphomas contribute to the majority (62%) of deaths in patients with APDS.[7] In addition, the accumulation of multiple APDS manifestations over time leads to a substantial and long-term impact on the quality of life (QoL) of patients. Disease manifestations begin within the first two years of life for most people with APDS.[8] Subsequent disease progression means that by the age of 12, almost all individuals have experienced respiratory infections, the vast majority have experienced lymphoproliferation and substantial proportions of the population have experienced gastrointestinal manifestations and cytopenia.[6] These manifestations are experienced despite currently available treatments,[3-6] and evidence indicates that these manifestations are associated with significant and lifelong QoL impacts.[9-15] People with APDS are unable to live a normal life due to: recurrent infections; feeling “always tired”, “exhausted” and “drained, both mentally and physically”; hospitalisations; the need to undergo tests and try new treatments; symptoms; and the impact of APDS on relationships and social life.[16, 17] According to clinical expert opinion, these testimonies are representative of almost all people with APDS.[14] Individuals with other inborn errors of immunity (IEIs) also have lower health-related quality of life (HRQoL) than healthy individuals.[18-22] Overall, Pharming believes that this criterion is met; available evidence shows that APDS significantly shortens life and severely impairs QoL. Decisions by EMA to grant Accelerated Assessment and MHRA to grant a Promising Innovative Medicine (PIM) designation are also supportive of APDS meeting this criterion.[23, 24] **Criterion 4: There are no other satisfactory treatment options in APDS, and leniolisib is likely to offer significant additional benefit over existing treatment options**	

Section	Stakeholder	Comments [sic]	Action
		There are currently no approved treatment options for APDS globally. Due to an absence of specific therapies that target the root cause of APDS (the hyperactive PI3Kδ pathway), individuals and clinicians use combinations of symptomatic treatments to manage individual manifestations or to manage the combined immunodeficiency and immune dysregulation.[5, 25] Current treatments are given in combination to attempt to address different disease manifestations. However, despite available treatments, patients continue to develop a range of manifestations and continue to have a shortened life expectancy.[3-6] Treatments are insufficient to resolve symptoms completely, and some patients continue to experience recurrent severe infections and/or exacerbations of lymphoproliferation, which are occasionally triggered by EBV infections.[2] In addition, these treatments are often accompanied by frequent and life-threatening adverse events (AEs).[3, 4, 6, 26, 27] Where symptomatic treatments cannot manage disease manifestations and symptoms at a tolerable level, where life-threatening episodes of lymphoproliferation occur, or where there is a need to reduce an individual's risk of developing lymphoma, haematopoietic stem cell transplantation (HSCT) currently remains the last option. However, HSCT is not a satisfactory treatment option for people with APDS. Adverse complications (seen in ~90% of people) and engraftment failure (seen in up to 36.4%) are frequent and serious in people with APDS who have received HSCT, which has been shown to carry a 2-year mortality risk of 10–20%.[2, 28-31] For these reasons, HSCT use is restricted to people with APDS who have severe and complicated clinical manifestations, with no or insufficient response to the currently available conventional therapies. Adult patients tend to prefer alternative treatments due to the mortality and morbidity risks associated with HSCT.[30] Overall, Pharming considers that this criterion is met by leniolisib in APDS, as leniolisib has the potential to fill the unmet need for an effective, disease-modifying treatment with a tolerable safety profile, within a disease area with	Thank you for your comment. Comment noted.

Section	Stakeholder	Comments [sic]	Action
		no satisfactory or appropriate treatments. Decisions by EMA to grant Accelerated Assessment and MHRA to grant a PIM designation are also supportive of APDS meeting this criterion.[23, 24]	
Wording	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	NA	No action required
	Pharming Technologies BV	The wording of the draft remit implies that the marketing authorisation for leniolisib will be for 'untreated APDS'. Pharming would like to note that it is anticipated that leniolisib will be marketed for the treatment of APDS in adults and adolescents 12 years of age and older, with no restriction on whether patients have previously received any other form of treatment. The word 'untreated' should therefore be removed from the draft remit.	Thank you for your comments. The wording in the remit has been updated.
Timing issues	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	APDS is an ultra-rare disease with no approved therapies. There is an unmet need for treating the consequences of having a dysregulated immune system – autoimmunity, malignancy which Leniolisib can address, so this needs an urgent evaluation. The EMA Committee for Medicinal Products for Human Use (CHMP) has granted an accelerated assessment for the Marketing Authorisation Application (MAA) for leniolisib highlighting this is an important treatment option for this patient group.	Thank you for your comment. This evaluation has been scheduled into the work programme.

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	Pharming Technologies BV	Pharming believes that there is a high degree of urgency for NICE to conduct a technology evaluation for leniolisib in APDS. The need for accelerated processes for leniolisib has been recognised by both the EMA and FDA through their granting of an accelerated marketing authorisation assessment and priority review, respectively. These accelerated processes have been granted for leniolisib in recognition of its major interest for public health and significant expected improvement compared with current therapy considering the unmet need for a disease-modifying treatment in APDS.[23, 32] Available evidence shows that APDS severely impacts QoL through the accumulation of severe and recurrent disease symptoms within multiple organ systems, due to immune dysregulation and immunodeficiency. Disease complications may lead to the accumulation of irreversible damage, such as to the lungs in the form of bronchiectasis. Therefore, early treatment initiation would be in the interest of patients, to prevent irreversible organ damage; leniolisib would be able to provide a treatment option for people with newly diagnosed APDS. Long-term, some people with APDS have shortened life expectancy, for example as a result of malignant lymphoma; earlier treatment may reduce the risk of disease progression to lymphoma.[2, 4-6, 18, 29, 33, 34] APDS is a chronic disease, with individuals continuing to experience disease manifestations throughout their lifetime.[4-6] Individuals can require long-term therapy and frequent hospitalisations, necessitating lifelong support from the NHS.[4, 6, 35] Patients may also require close, multi-disciplinary monitoring as multiple organ systems become affected.[36] UK clinicians have reported that moving patients off immunoglobulin replacement treatment (IRT) is considered a significant achievement, both clinically and financially, indicating the importance of reducing long-term treatment requirements;[34] notably, [redacted].[37] It is therefore in the interest of the NHS, and people with APDS and their caregivers, that urgency is placed on the	Thank you for your comment. This evaluation has been scheduled into the work programme. Thank you for your comment. comment noted.

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		evaluation for leniolisib, to limit the future treatment requirements for patients and the corresponding costs. There are currently no approved treatments for APDS globally, nor any targeted therapies known to be in development beyond leniolisib. Individuals receive combinations of non-specific immunosuppressive and symptomatic treatments which do not target the underlying cause of the disease.[5, 25] Despite available off-label treatments, patients continue to develop a range of manifestations.[3-6] In addition, these treatments are often accompanied by frequent and life-threatening adverse events (AEs).[3, 4, 6, 26, 27] HSCT is associated with severe adverse complications and a mortality risk of 10–20%, and fails to address non-haematologic manifestations of APDS such as renal complications.[29-31] For these reasons, it is only used in 9–13% of patients with APDS,[31] primarily people who have severe and complicated clinical manifestations, with no or insufficient response to the currently available conventional therapies. Based on the absence of appropriate, approved therapies for APDS, there is a need to ensure that timely access to a disease-modifying treatment is achieved. **In summary, there is an urgent need for a disease-modifying treatment for people with APDS, and leniolisib is currently the only known treatment being developed to fulfil this significant unmet need.**	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.
Additional comments on the draft remit	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	NA	No action required

Section	Stakeholder	Comments [sic]	Action
	Pharming Technologies BV	NA	No action required

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Genetic Alliance UK	APDS is a condition that presents from childhood and having frequent infections due to their condition is likely to impact a child's ability to regularly attend school, therefore impacting their education and employment opportunities in the future. This also impacts a child's ability to interact and form relationships with peers, negatively impacting their overall wellbeing. When determining severity, it is important to consider that family life can be disrupted by having a child with significant health needs who will likely need many trips to doctors and hospitals for ongoing and emergency care for frequent infections. The financial burden of travel costs to far away hospitals and missing work puts pressure on affected individuals and their families. Parents may have to stay overnight and this can make it difficult for both parents to maintain a full time job; parents may have to limit their working hours to ensure their child can get to the hospital which may exacerbate the financial position of the family. The rising concern of antimicrobial resistance means that the risk of serious illness from infections is constantly increasing and this can be emotionally difficult for families to deal with.	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Affected individuals will often try to limit their exposure to bacteria and viruses which may include limiting their contact with other people, therefore impacting their emotional wellbeing.	
	Immunodeficiency UK	This is very light touch. There is no mention of APDS1 (PIK3CD) and APDS2 (PIK3R1) subtypes. It is our understanding that Leniolisib is only for APDS1 whereas its role in PI3KR1 (APDS2) is yet to be determined. It is a severe immunodeficiency that results in increased morbidity and mortality rates. Diagnostic delay diagnosis can negatively affect prognosis. Patients with APDS may have to undergo splenectomy due to cytopenia or splenomegaly. A significant proportion of younger patients, < 12years, have had tonsillectomy. There is no mention of skin complications such as herpes and eczema which may affect about 40% of patients with APDS1. These skin conditions can add to social stigma and reduced quality of life. Bronchiectasis is a frequent complication in APDS – about 40% of patients are affected. Bronchiectasis can be life-limiting and life threatening, impact severely on quality of life and can occur in early childhood.	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Immunoglobulin (IG) therapy is used in combination with antimicrobials to manage and reduce infections potentially stopping progression of bronchiectasis due to reduction in respiratory tract infections, as well treating antibody deficiency. Some patients will have poor vaccine responses due to their antibody deficiency.	
	Pharming Technologies BV	Currently, Pharming feels that the background information does not sufficiently capture the full known extent of APDS and the inadequacy of current off-label treatments in APDS. There are also a number of technical inaccuracies. Please could the following be acknowledged or made clearer within paragraph 1, of the background information: • Genetic variants in APDS can occur through inheritance of variants, or through **development of variants *de novo***.[38] Several analyses have shown that APDS variants have also appeared *de novo* in children, with no corresponding variants in their parents.[25] Under current medical terminology, APDS is considered an **inborn error of immunity** (otherwise referred to as a primary immunodeficiency).[39] • The paper by Fruman DA, et al., entitled 'The PI3K Pathway in Human Disease' may be a more appropriate reference, for evidence supporting the link between PI3Kδ overactivation, and aberrant B and T cell development.[40] • APDS is characterised by both immune deficiency **and immune dysregulation**, with implications for both frequent infections **and autoimmune complications.**[5] Pharming would recommend expanding on the description of APDS	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		(within the first sentence) to capture both aspects of its impact on immune function. • Comprehensive supportive evidence for the main manifestations of APDS has been provided by the papers by Coulter et al., Maccari et al., and Jamee et al.[4-6] • APDS is a **complex and progressive disease**, with people experiencing chronic symptoms from disease manifestations within **multiple organ systems**, including the sinopulmonary, lymphatic, immune, gastrointestinal and neurological systems. In addition to the symptoms already listed in the background information, Pharming requests the addition of: **bronchiectasis, nodular lymphoid hyperplasia, allergies, and impaired cognitive development**. It should also be noted that the infections experienced by people with APDS are **severe and persistent.**[3-6] • Approximately 50% of people with APDS experience lower-than-normal levels of blood cells, in a condition called cytopenia.[6] Pharming would recommend clarifying that 'lower-than-normal levels of blood cells' refers to cytopenia specifically. • The median age at the onset of symptoms is 1.7 years, and the **first clinical manifestations in most people** are recurrent infections or lymphadenopathy (swelling of lymph nodes). In later childhood, individuals may experience a range of additional autoimmune and autoinflammatory manifestations. Most people with APDS rapidly develop manifestations in the first five years of their life.[5, 6, 41]	

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		• Recurrent infections can cause **permanent damage,** for example to the ears and lungs, with bronchiectasis prevalence as high as 60%.[4, 42] By late adolescence, people with APDS are at a high risk of developing lymphomas, with lymphoma-free survival falling to approximately 22% by age 40, and other malignancies such as acute myeloid leukaemia reported.[3, 5] • Available evidence shows that APDS **severely impacts QoL** of people with APDS and their caregivers[42] through the accumulation of disease complications and recurrent infections. Available studies and reviews have reported 40-year survival estimates ranging from 86% to <60%, with early mortality caused by malignancies and non-malignant diseases, such as cardiopulmonary arrest, bowel perforation, septic shock, multiple organ failure and pulmonary haemorrhage.[2, 4-6, 18, 29, 33] Please could the following be acknowledged or made clearer within paragraph 2, of the background information: • Whilst Pharming agree with the epidemiology estimate presented, it is worth noting for context that APDS therefore represents a **'very rare' condition**. Please could the following be acknowledged or made clearer within paragraph 3, of the background information: • Current treatments are used off-label, and are non-specific immunosuppressive and **symptomatic** treatments, which do not target the underlying cause of the disease. No existing treatments address the hyperactive signalling in the PI3Kδ pathway, and therefore no existing treatments can address	Thank you for your comment. The wording has been updated in the final scope. Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		both the immunodeficiency and immune dysregulation associated with APDS. It should be noted that APDS manifestations **progress despite the use of current treatments.**[3-6] The study of people with APDS by Okano et al. summarises the lack of satisfactory, appropriate, disease-modifying treatment options: more than 90% of participants had persistent symptoms despite treatment.[2] • Existing treatments are also associated with frequent and life-threatening **adverse events.**[3, 4, 6, 26, 27]	
Population	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	Need to define APDS1 and APDS2 cohorts clearly.	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.
	Pharming Technologies BV	We can confirm that the wording describing the population is appropriate. The anticipated marketing authorisation wording is outlined in Comment 4. We consider this wording more appropriate than the wording of the draft remit, as mentioned in Comment 1 above.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
Subgroups	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	NA	No action required
	Pharming Technologies BV	Not applicable.	No action required
Comparators	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	Clinical heterogeneity of APDS means that treatment needs to be tailored carefully to each patient's needs. The treatments listed are used within the NHS to treat APDS. HSCT can be curative but not suitable for all APDS patients and long-term follow-up data is needed. It has been used for about 10% of patients to treat life threatening infections and as part of treatment for lymphoma. The procedure has a 10-20% mortality risk and can be complicated by existing co-morbidities and active, uncontrolled manifestations of immune dysregulation. It remains unclear as to if, and when to perform a HSCT for APDS. HSCT is also dependent on having a good tissue match and this may not be possible for some patients. Antimicrobials are used in about 60-80% of patients. Most commonly antibiotics but can include anti-fungal as well as anti-virals. IG	Thank you for your comment. The comparator in the scope is established clinical management without leniolisib and is broad to allow consideration of the variety of treatment options which may be offered in current care.

Section	Consultee/ Commentator	Comments [sic]	Action
		therapy is used for about 75% of patients. These therapies do not prevent herpes infections, autoimmunity and lymphoproliferation. Steroids and rituximab treatment may increase susceptibility to infections and use needs to be carefully managed.	
	Pharming Technologies BV	Pharming is in agreement with established clinical management forming the comparator, but would like to discuss whether the word "established" is appropriate (see "Any additional comments on the draft scope"). There are no approved pharmacological treatments for APDS. Based on feedback from expert clinical immunologists, the typical care pathway in the UK includes symptomatic treatments such as antimicrobial therapies (antibiotics, antifungal and antiviral drugs), IRT, and immunosuppressive treatments including corticosteroids, as well as mammalian target of rapamycin (mTOR) inhibitors (primarily sirolimus) and rituximab.[5, 25] HSCT is restricted to people who have severe and complicated clinical manifestations, with no or insufficient response to the currently available conventional therapies.[14] Please see "Questions for Consultation" for a summary of the treatments that are in use in NHS clinical practice for the treatment of APDS.	Thank you for your comment. The comparator in the scope is established clinical management without leniolisib and is broad to allow consideration of the variety of treatment options which may be offered in current care.
Outcomes	Genetic Alliance UK	Quality of life of not just the individual but that of family and carers should also be considered. As described above, this condition significantly impacts people who are close to affected individuals.	Thank you for your comment. Comment noted.
	Immunodeficiency UK	Yes, but could also consider: • Reduction of senescent T cells • Reduction of markers of inflammatory and autoimmune complications • Reduction of thrombocytopenia	Thank you for your comment. The outcomes in the scope have been amended based on consultation comments and

Section	Consultee/ Commentator	Comments [sic]	Action
		Impact on skin and colitis complications – both of which can significantly affect quality of life. Leniolisib may reduce the need for HSCT, but whether or not it is a lifelong solution in a child presenting at a young age is unclear.	feedback heard at the scoping workshop
	Pharming Technologies BV	Pharming considers the outcome measure listed in the draft scope as appropriate and relevant. However, Pharming would suggest grouping some of the outcomes as follows: • Immunophenotype measures (including lymphocyte counts [such as naïve B cells], immunoglobulin levels, and cytokine and chemokine levels) • Immune system function (including lymphadenopathy [lymph node size], organomegaly [spleen and liver volume size], infections, use of IRT) • Fatigue • Mortality • Disease severity • Adverse and serious effects of treatment • Health-related quality of life	Thank you for your comment. The outcomes in the scope have been amended based on consultation comments and feedback heard at the scoping workshop.
Equality	Genetic Alliance UK	NA	No action required.
	Immunodeficiency UK	There are no specific ethnic groups that are affected by APDS.	Thank you for your comment. comment noted.

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	Pharming Technologies BV	Pharming believes that NICE's preliminary decision to route this evaluation through the STA programme, rather than the HST programme, may raise considerations in relation to equity. Routing the evaluation via the STA programme does not fully account for the challenges inherent to a very rare condition (such as the limited evidence base in APDS), or the substantial unmet need, as recognised by the EMA's orphan designation.[1] This creates a lower likelihood for leniolisib of being cost-effective at the lower willingness-to-pay threshold within the STA vs HST programme, despite recognition of leniolisib by the EMA as an innovative therapy of major public health interest,[23] and by the MHRA as a product likely to offer a major advantage over methods currently used in the UK.[24] Therefore, Pharming have concerns that routing a product for a very rare condition – with a significant unmet need and disease severity – through the STA programme, would result in **a lower and unequal potential for access** when compared to products for conditions with a much higher prevalence and more established evidence base. Pharming also have concerns that routing to the STA programme and the resulting required evidence base will result in further delays in the advancement of the only known, disease-modifying treatment in development for APDS, in light of the need for timely access to treatment as described in Comment 1. Finally, current clinical management for APDS is based largely on off-label therapies, without any formal treatment guidelines, which may lead to inconsistency in care across people with APDS. Therefore, there is a high need for national commissioning with appropriate NICE guidelines in place, to ensure that all individuals	Thank you for your comment. The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a highly specialised technology evaluation.

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		with APDS in the UK follow a consistent care pathway and have equal access to a treatment approved for APDS.	
Other considerations	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	NA	No action required
	Pharming Technologies BV	Not applicable.	No action required
Questions for consultation	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	There are approximately 20 APDS patients in England. We have no knowledge of the breakdown into APDS1 and APDS2 cohorts. Figures quoted online indicates that Leniolisib could be suitable for about 25% of APDS patients. Mortality and age of patient data is available via UKPIN and ESID APDS registries and through the resulting publications. Incidence of infections, manifestations and their evolution in APDS patients, and treatment modalities are summarised in Maccari et al., https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863269/ (Figures 1 and 2). The main cause of mortality is lymphoma and its complications or treatment.	Thank you for your comment. Comment noted.

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		Diagnosis Onset of disease can be variable over time, both in terms of age at presentation and in terms of clinical and immunological complications. Many people are diagnosed in childhood but there is a small minority of patients who will be diagnosed in adulthood. In many cases, patients are referred to various specialists such as haematologists, rheumatologists, gastroenterologists, and others, before an immunological evaluation is done, leading to delay in diagnosis (reported to be in the order of seven years), which can negatively affect prognosis. APDS can be misdiagnosed – patients within CVID and CID cohorts have been found to have APDS. Under-diagnosis is a common occurrence for many rare disorders. **Testing for APDS** Genetic testing provides a definitive diagnosis of APDS. The genes are on the R15 panel on panel app and testing is therefore standard **if undertaking genetics for PID**, Primary immunodeficiency or monogenic inflammatory bowel disease (Version 3.1) (genomicsengland.co.uk). Family members of a confirmed patient should always be genetically tested. **Quality of life issues** There is a significant burden on quality of life of those affected. It can be challenging living with frequent infections, managing treatment regimes, and attending multiple appointments, often with different medical specialities with the associated financial impact of taking time off work and the cost of travel to hospital. Patients can require hospitalisation and some patients report spending months in hospital.	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Comment noted. These aspects will be considered further in

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		People with APDS report extreme exhaustion - 'drained both mentally and physically', 'always tired'. Living with chronic lung disease also adversely affects quality of life. There can be pain due to gastrointestinal problems, with bouts of diarrhoea meaning daily life can revolve around planning for the nearest toilet. This can affect people wanting to socialise and forming relationships. Gastro-intestinal problems can lead to malabsorption and being underweight. There can be feelings of isolation and frustration at always having to explain their condition and its health impacts. There can be fear about what the future looks like due to patient awareness about the longer-term consequences of having a dysregulated immune system – autoimmunity, malignancy. We are not aware of specific QoL studies in APDS patients but relevant information on the impact of living with a primary immunodeficiency and bronchiectasis can be found in these references: Health-related quality of life in patients with primary immunodeficiency disease - PMC (nih.gov) Increased Incidence of Fatigue in Patients with Primary Immunodeficiency Disorders: Prevalence and Associations Within the US Immunodeficiency Network Registry | SpringerLink Paediatric and adult bronchiectasis: Diagnosis, disease burden and prognosis - Quint - 2019 - Respirology - Wiley Online Library	evidence submission and by the committee.

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	Pharming Technologies BV	Are any of the following treatments used to treat APDS in the NHS as standard practice? • Haematopoietic stem cell transplantation • Immunoglobulin Replacement Therapy (IRT) • Steroids • Mammalian target of rapamycin (mTOR) inhibitors • Rituximab • Antimicrobials Given the wide range of clinical manifestations of APDS and the very recent identification of APDS as a unique disease, there are no formal guidelines on how to treat APDS in the UK. Nonetheless, clinical experts confirm that current treatment options for APDS include antimicrobial therapies (antibiotics, antifungal and antiviral drugs), immunoglobulin replacement therapy (IRT), and immunosuppressive treatments including corticosteroids, mammalian target of rapamycin (mTOR) inhibitors (primarily sirolimus) and rituximab.[5, 14, 15, 25] Treatments are dependent on manifestations and symptoms. For example, those presenting with mostly respiratory infections would be treated with antibiotic prophylaxis and IRT.[34] Those presenting with autoimmune manifestations, such as cytopenias, would be treated with immunosuppressants such as corticosteroids or rituximab.[6, 34] mTOR inhibitors may temporarily reduce the severity of	Thank you for your comment. Comment noted.

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		lymphoproliferative disease.[6] Clinicians will use a combination of treatments depending on an individuals' symptoms. HSCT has only been used to treat 9–13% of patients with APDS, indicating low uptake in clinical practice.[31] Due to high rates of adverse complications (seen in ~90% of people), and the high risk of engraftment failure (seen in up to 36.4% of people),[29-31] HSCT use is restricted to people with APDS who have severe and complicated clinical manifestations, with no or insufficient response to the currently available conventional therapies (i.e., according to a UK clinician, once they have already established structural end organ damage [e.g. bronchiectasis] or severe clinical manifestations [e.g. lymphoma]).[14] These patients must also be aged 25 years or less, otherwise HSCT is not commissioned outside of cancer pathways. However, by the age of 25, individuals are likely to have already developed complications of APDS, co-morbidities, or be unwilling to undergo this risky procedure, due to concerns about leaving behind dependents.[14].[34] Additionally, HSCT fails to address non-haematologic manifestations of APDS such as renal complications.[30] In summary, HSCT is restricted to a small subgroup of people with APDS due to the risk of poor outcomes. How many people have APDS in England, and how many would be offered leniolisib? Based on the prevalence of APDS in the EU (1 in 1,000,000), a population size of approximately 56.6 million in England, and a population growth rate of 0.47% (mid-2020 figures),[43] Pharming estimate that there would be no more than 60 people with APDS in England. As leniolisib will be licensed for patients aged 12 years and over, it is anticipated that fewer than 60 people would be offered leniolisib in England.	Thank you for your comment. Comment noted.

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		Are the genetic tests to establish the correct diagnosis of APDS a standard practice in the NHS?	
		Yes, genetic tests are available for APDS and part of standard practice in the NHS.[44]	Thank you for your comment. Comment noted.
		Where do you consider leniolisib will fit into the existing care pathway for APDS?	
		It is likely that the timing of the use of leniolisib would be down to physician choice (as is the case for current APDS treatments). Nonetheless, given the risks from a young age of long-term organ damage and lymphoma with APDS, Pharming anticipates that leniolisib, as the first disease-modifying therapy entering the treatment landscape for APDS, would be used as the first line of treatment after diagnosis.	Thank you for your comment. Comment noted.
		Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope?	
		Please see the response from Pharming in Comment 2, above, regarding outcomes.	Thank you for your comment. Comment noted.
		Is there any data/evidence available on how long people live with APDS/the impact of APDS on quality of life?	
		Available evidence shows that APDS significantly shortens life and severely impairs QoL.	
		Please see the response from Pharming in Comment 1 (above), outlining evidence that leniolisib meets criterion 3 for the HST programme. Please also see Pharming's response to the HST criteria checklist for detailed evidence.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups of people in whom leniolisib is expected to be more clinically effective and cost effective or other groups that should be examined separately? There is no evidence to suggest that leniolisib would be more clinically or cost effective in any subgroups of people with APDS. Do you consider that the use of leniolisib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. • Current treatments are symptomatic and do not target the underlying disease; therefore, people with APDS are often required to take concomitant medication (for example, IRT alongside antimicrobials), with implications for administration burden and combined adverse effects. [redacted] • In addition to polypharmacy [redacted] • Behaviours to prevent recurrent respiratory tract infections impact on quality of life. People with APDS have noted the need to be mindful about what they eat and drink.[10] By reducing the need for lifestyle adjustments to avoid infections, treatment with leniolisib may enable patients to lead less restricted lives.	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted]*[redacted].[45, 46] This benefit may be particular beneficial in the case of any future epidemics or pandemics, since people with APDS are particularly vulnerable to infection. • Intravenous IRT can take up to 8 hours per 4 weeks and subcutaneous injection takes up to approximately 4 hours every week,[47] and patients and caregivers spend long periods of time travelling to and from infusion sites every two to four weeks.[35] This time spent represents an opportunity cost; travel may also be associated with out-of-pocket costs for patients and caregivers. [redacted]*	
Additional comments on the draft scope	Genetic Alliance UK	NA	No action required
	Immunodeficiency UK	NA	No action required
	Pharming Technologies BV	• Pharming wanted to note at this stage that leniolisib will be investigated in patients aged 4–11 years of age [redacted]	Thank you for your comment. Comment noted. The evaluation will consider the population in

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] • [redacted] • Pharming would also like to discuss at the scoping workshop whether the term “established” is appropriate for describing clinical management in APDS, given the absence of any formal consensus guidance on clinical management for APDS, and possible variation in the clinical pathway.	line with the marketing authorisation. Thank you for your comment. This was discussed during the scoping workshop and TSOP also acknowledged that there are no licenced or NICE-approved treatment options available for APDS. People rely on current treatments based on presentation and there are unmet needs for people with APDS.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Neonatal and Paediatric Pharmacy Group (NPPG)