5.07 LENIOLISIB, Tablet 70 mg, Joenja®, Pharming Australia Pty Ltd

1 Purpose of submission

1.1 The Category 1 submission requested listing of leniolisib on a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for the treatment of symptomatic activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adults and adolescents aged 12 years and older.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC). SoC refers to a range of treatments currently used in Australia to manage symptoms of APDS.

1.3 The submission proposed leniolisib be considered for listing on either the PBS or under the Life Savings Drugs Program (LSDP). The PBAC noted it does not make recommendations or give advice to the Minister about which drugs should be listed on the LSDP.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Individuals with symptomatic[a] activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) aged 12 years and over
Intervention	Leniolisib (70mg film-coated tablet for oral administration), BD plus standard of care
Comparator	Placebo/best supportive care (standard of care)
Outcomes	• Mortality • Malignancy (particularly lymphoma) • (Advanced) lung disease, decline in lung function and recurrent pneumonia leading to bronchiectasis-associated airway disease • Infections causing frequent hospital admissions • Lymphoproliferation • Gastrointestinal symptoms (resembling IBD) • Hearing loss • Immune system function • Immunophenotype measures (lymphocyte counts, cytopenia, immunoglobulin levels, cytokine and chemokine levels, use of IRT and antibiotics) • Lymph node size, spleen and liver volume size
Clinical claim	Leniolisib has superior efficacy and non-inferior safety relative to standard of care

APDS = activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome; BD = twice daily; IBD = inflammatory bowel disease; IRT = immunoglobulin replacement therapy; mTOR = mammalian target of rapamycin; PI3Kδ = phosphoinositide 3-kinase delta

[a] Symptomatic is defined a demonstrated mutation in either the *PIK3CD* or *PIK3R1* genes associated with APDS and having documented APDS associated symptoms or have been receiving any form of intervention to manage APDS (eg prophylactic antibiotics, IRT, mTOR inhibitors, immunosuppressive therapies). The purpose of this restriction is to exclude those people who are asymptomatic carriers.

Source: Table 1.1, p25 of the submission.

2 Background

Registration status

2.1 Leniolisib was TGA registered on 18 March 2025 for the treatment of APDS in adults and adolescents 12 years of age and older.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
LENIOLISIB					
Leniolisib, 70mg, tablet for oral administration	$[redacted] published price $[redacted] effective price (Public Hospital)	1	60	5	Joenja Pharming Technologies BV

Source: Table 1.6, p59 of the submission.

Category / Program: Section 100 (HSD Program); Life Saving Drugs Program
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)*
Indication: Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)
Treatment Phase: Initiation
Clinical criteria:
Patient must have a diagnosis of APDS, confirmed by genomic or genetic testing demonstrating a pathogenic or likely pathogenic gain-of-function variant in the *PIK3CD* gene or a pathogenic or likely pathogenic loss-of-function variant in the *PIK3R1* gene
AND
Confirmation of symptomatic APDS, defined as having required or currently requiring any kind of therapeutic intervention for control or prevention of APDS-associated complications based on specialist clinical assessment. Clinical assessment tests may include: 1. Immunological evaluations: White blood cell count, lymphocyte count, lymphocyte subset analysis, serum IgG/IgG2/IgA/IgM, T-cell receptor excision circles (TRECs) and KRECs (Igκ -deleting recombination excision circles). 2. Monitoring of EBV/CMV infections: EBV-related antibody titre, CMV antigenemia test, blood EBV/CMV viral load assay. 3. Pulmonary function tests: Bronchiectasis due to repeated lower respiratory tract infections should be carefully monitored. Chest X-rays and chest CT scans should be evaluated as necessary. 4. Evaluation of lymphoid hyperplasia: Examine for tonsils and superficial and deep lymph nodes and hepatosplenomegaly, with assessments of imaging tests (i.e., CT/MRI, FDG-PET) as necessary. 5. Surveillance of malignant tumours: Carefully monitor for development of lymphoma. 6. Evaluations of other complications: Examine for enteropathy including the gastrointestinal fibre scope. Type 1 diabetes mellitus can be associated with APDS2.
Treatment criteria:
Leniolisib should be prescribed by or in consultation with an immunologist with expertise in managing patients with primary immunodeficiencies or APDS specifically.
AND
Patient should not be receiving concomitant treatment with any of the following: (i) rituximab; (ii) mTOR inhibitors
Population criteria:
Patients must be aged 12 years or over
Prescribing Instructions: Authority applications for initial treatment must be made in writing and must include: (a) Details of the proposed prescription; and (b) A completed authority application form, relevant to the indication and treatment phase, which includes the following: (i) Report confirming evidence of APDS with genetic diagnosis (as outlined under Clinical criteria) for gain of function mutations around *PIK3CD* and *PIK3R1* (ii) Details (clinical history summary, any other testing, scans or imaging performed) of demonstration of symptomatic APDS (as per clinical criteria).
Patient should be reviewed at 5 months after treatment initiation for treatment failure and meeting the continuation criteria for continuation of therapy after 6 months of initial treatment (application will need to be done by start of sixth month of therapy to ensure continuation of therapy from month 7)
If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, please provide details of the degree and nature of this toxicity
Administrative Advice: Maximum duration of initial authorisation is six months

*The submission stated that the submission type was "Authority Required (s100)", but under prescribing instructions stated that Authority applications for initial treatment must be made in writing.
Source: Table 1.7, pp61-62 of the submission.

Category / Program: Section 100 (HSD Program); Life Saving Drugs Program
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists
Restriction type: ☒Authority Required*
Indication: Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)
Treatment Phase: Continuation
Clinical criteria:
Previous treatment with leniolisib for APDS under initiation criteria
AND
Clinical confirmation that APDS symptoms have been managed (as defined by limiting progression of symptoms and/or resolution of symptoms) following the initial treatment period of six months. This should be assessed by or in consultation with an immunologist with expertise in managing patients with inborn errors of immunity, or APDS specifically.
Treatment criteria:
Aligned to initiation criteria; Leniolisib should be prescribed by or in consultation with an immunologist with expertise in managing patients with inborn errors of immunity, or APDS specifically.
AND
Patient should not be receiving concomitant treatment with any of the following: (i) rituximab; (ii) mTOR inhibitors
Population criteria:
Patients must be aged 12 years or over

*The submission did not provide any further details regarding the type of Authority Required restriction.
Source: Table 1.8, pp63-64 of the submission.

Category / Program: Section 100 (HSD Program); Life Saving Drugs Program
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists
Restriction type: ☒Authority Required (s100)*
Indication: Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)
Treatment Phase: Reinitiation
Clinical criteria:
Previous treatment with leniolisib for APDS under initiation criteria
AND
Clinical confirmation that APDS symptoms have previously been managed (as defined by limiting progression of symptoms and/or resolution of symptoms) following initial treatment
Treatment criteria:
Aligned to initiation criteria; Leniolisib should be prescribed by or in consultation with an immunologist with expertise in managing patients with inborn errors of immunity, or APDS specifically.
AND
Patient should not be receiving concomitant treatment with any of the following: (i) rituximab; (ii) mTOR inhibitors
Population criteria:
Patients must be aged 12 years or over

*The submission did not provide any further details regarding the type of Authority Required (s100) restriction.
Source: Table 1.9, pp64 of the submission.

3.1 The submission proposed an effective ex-man price of $[redacted] per pack (60 tablets) ([redacted]% less than the proposed public list price of $[redacted] per pack). The pre-PBAC response proposed a revised effective ex-man price of $[redacted] per pack.

3.2 The requested restriction was mostly consistent with the TGA approved indication, except that patients must have APDS that is symptomatic to initiate treatment with leniolisib (i.e. narrower than the TGA indication). The submission stated that the intention was to exclude asymptomatic or "carrier" patients.

3.3 The proposed restriction criteria state that the patient must have a diagnosis of APDS confirmed by genomic or genetic testing, however a corresponding test/panel is not funded through the MBS for patients aged more than 10 years. The submission claimed that genetic testing for patients for inborn errors of immunity (IEIs) such as suspected APDS, is funded free of charge through public hospital systems for the purpose of diagnosis, however the evaluation noted that for adult patients in the private system there may be out of pocket costs, as confirmed in consultation with Australian clinicians and the Australasian Society of Clinical Immunology and Allergy (ASCIA). The Pre-Sub-Committee Response (PSCR) noted that on 10 March 2025, the ASCIA lodged a letter of support for an MSAC application by the Royal College of Pathologists of Australasia (RCPA) for genomic testing for the diagnosis of IEI, including primary immunodeficiency diseases (PID). The PBAC agreed with its Sub-Committees (ESC and DUSC) and considered that genetic testing is not a barrier to APDS diagnosis and while the test is not on the MBS, all patients currently have access to testing given APDS patients are mainly treated in public hospitals by a small number of clinicians.

3.4 The proposed initiation criteria required confirmation of symptomatic APDS, defined as having required or currently requiring any kind of therapeutic intervention for control or prevention of APDS-associated complications based on specialist clinical assessment. While the proposed wording states that 'confirmation of symptomatic APDS' was required, no examples of symptoms were provided and instead, a range of clinical assessment tests were listed. Patients with APDS are typically identified as potentially having an IEI based on symptoms/presentation before they undergo functional laboratory testing and identification of the specific IEI. Therefore, it was likely that all patients being considered for treatment with leniolisib would have demonstrated prior symptoms. The Sub-Committees noted the testing requirements were consistent with trial eligibility criteria but considered it remains unclear which (if any) assessments should be required to confirm diagnosis/symptoms and whether the proposed criteria would be reasonably expected to identify patients with symptoms and manifestations consistent with patients included in the clinical trials.

3.5 The proposed initiation restriction did not include any requirement for patients to be naïve to leniolisib treatment. Therefore, patients receiving leniolisib under the leniolisib early access program (EAP), or patients who had previously received treatment under the EAP, would be able to initiate PBS subsidised treatment with leniolisib under the proposed initial treatment phase. The PBAC considered this would be reasonable. The PBAC also noted the switch from the EAP to PBS-funded leniolisib would not require demonstration of any response to or benefit with leniolisib, but ongoing treatment would require stable or responding disease.

3.6 While the proposed continuation and reinitiation criteria included the requirement for clinical confirmation that APDS symptoms have previously been managed following initial leniolisib treatment (as defined by limiting progression of symptoms and/or resolution of symptoms), no specific tests or explicit evidence of this was required. Consequently, it would largely be at the treating clinician's discretion whether a patient met the continuation criteria.

3.7 The submission proposed reinitiation criteria requiring patients to have received previous treatment with leniolisib under the initiation criteria. This reinitiation criteria would not be needed if patients who had previously had stable/responding disease while treated with leniolisib were able to access treatment under the proposed continuing restrictions.

3.8 The submission did not explicitly propose an authority level for the initial, continuing and re-initiation treatment phases, but alluded to a requirement of an "in writing" application in the prescribing instructions for the initial treatment phase, to confirm diagnosis of symptomatic APDS. In addition, patients who have met the eligibility criteria for ongoing treatment would need to provide details of an assessment of response to continue PBS-subsidised treatment with leniolisib.

3.9 The submission proposed immunologists or medical practitioners in consultation with an immunologist with expertise in managing patients with primary immunodeficiencies or APDS specifically as authorised prescribers. The Sub-Committees advised this would be appropriate given immunologists are responsible for of diagnosis/treatment for patients with IEIs.

3.10 The PBAC considered a Section 100 HSD listing (public/private hospital) appropriate to allow genetic/genomic diagnostic testing to be completed within the hospital setting.

3.11 The PBAC noted leniolisib as a first line treatment option, could also be used concomitantly with most existing SoC therapies (i.e. antimicrobials and/or immunoglobulin replacement therapy (IRT) and/or corticosteroids) for APDS, except with immunosuppressive medications such as rituximab and mTOR inhibitors, as proposed in the restrictions. The PBAC noted this was also consistent with Study 2201.

For more detail on PBAC's view, see section 7 PBAC outcome.

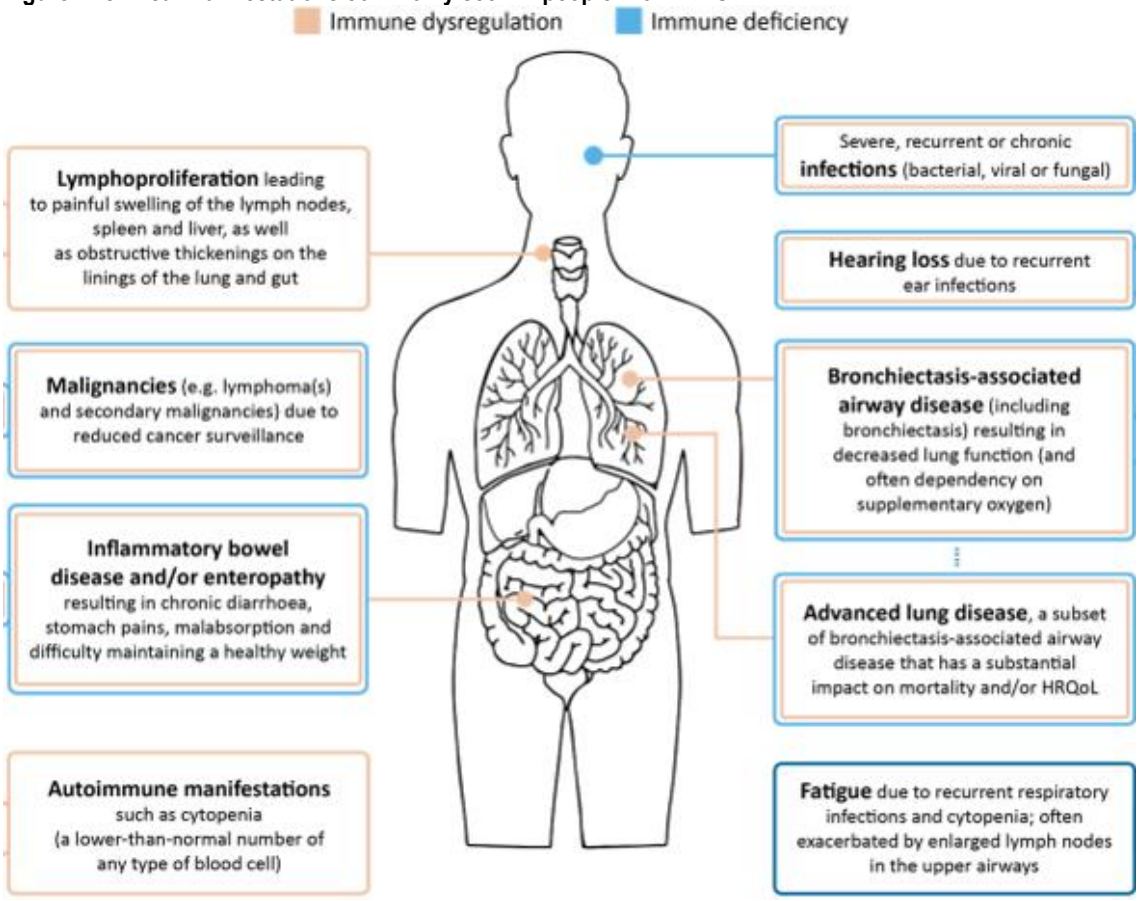
4 Population and disease

4.1 APDS is an ultra-rare severe IEI that affects the body's immune system. APDS is characterised by the dysregulation of the PI3Kδ signalling pathway, which has detrimental effects on the development and maturation of B and T cells, thereby impairing their functioning. The PI3Kδ protein complex comprises a p110δ catalytic subunit and a p85α regulatory subunit. The associated hyperactivation of the PI3Kδ pathway is caused by a pathogenic variant in either the PIK3CD or

PIK3R1 genes, with heterozygous gain-of-function mutations in PIK3CD affecting the p110δ catalytic subunit and heterozygous loss of function mutations in PIK3R1 affecting the p85α regulatory subunit.

4.2 People with APDS show symptoms of both overactive and underactive immunity. The combination of immune dysregulation and immune deficiency that occurs in patients with APDS leads to severe and potentially life-threatening multi-system manifestations. APDS has a heterogeneous presentation, as summarised in Figure 1. Symptoms can include recurrent infections, bronchiectasis, poor response to vaccination, abnormal phenotypes in immunoglobulin G (IgG) and blood cells, splenomegaly, lymphadenopathy, autoimmune cytopenia and a high risk of lymphoma.

Figure 1: Clinical manifestations commonly seen in people with APDS



APDS = Activated PI3Kδ syndrome; HRQoL = health-related quality of life.
Source: Figure 1.2, p31 of the submission.

4.3 The first symptoms of APDS usually occur early in life with >70% of patients experiencing symptoms when aged one to five years and >90% of patients experiencing symptoms when aged six to ten years (Thalhammer 2021). First symptoms are commonly related to infections (75.5%, particularly respiratory tract infections [65.0%]), organomegaly (15.8%), chronic diarrhoea or

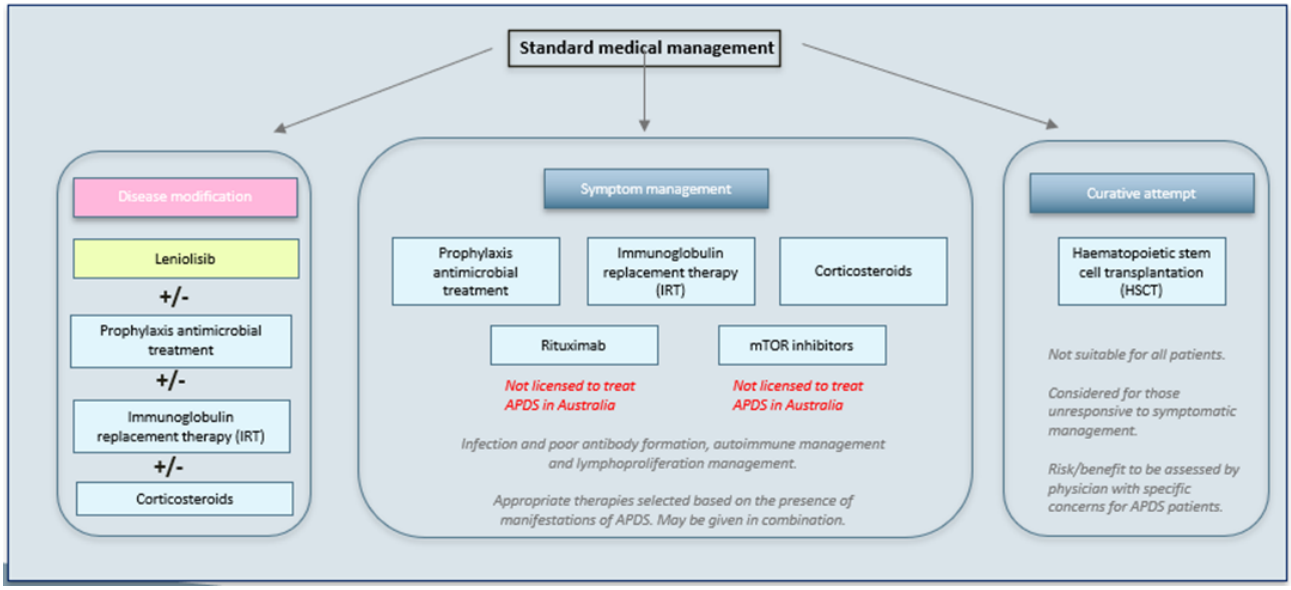
enteropathy (12.3%) or failure to thrive (8.8%) (Jamee 2020). APDS is progressive and patients experience additional manifestations as they get older. By adolescence, the majority of patients with APDS will experience multiple, life-limiting manifestations. Malignancy, and in particular lymphoma, is a major complication of APDS. The median age at presentation of malignancy is 18 years (Jamee 2020). The Sub-Committees also noted that bronchiectasis is also a major complication of APDS, is largely irreversible and can also be life-limiting.

4.4 Accumulation of severe manifestations, increased risk of malignancy and the adverse effects of current treatments all contribute to early mortality in APDS. Data from the European Society for Immunodeficiencies (ESID)-APDS registry reported that APDS patients had a 45% mortality rate at age 40, a 63% mortality rate at age 45 and a median survival age of 44 years (Maccari, unpublished manuscript). A systematic literature review identifying APDS patients found that lymphoma was the most common cause of death (with a mortality rate of 47.6%), followed by complications resulting from haematopoietic stem cell transplantation (HSCT; Hanson 2024). HSCT is an alternative non-drug therapy and potentially curative treatment for APDS. The Australasian Society of Clinical Immunology and Allergy (ASCIA) IEI Clinical Care Standard recommend consideration of HSCT for patients diagnosed with the most severe IEIs, however the submission noted that HSCT is not suitable or recommended for all patients and claimed that clinical experts have advised its use is not common practice in Australia.

4.5 Leniolisib is the first disease-modifying therapy (DMT) available for the treatment of APDS and is therefore likely to be used as a first line treatment option and as an add-on to existing Standard of Care (SoC) therapies for APDS. The evaluation noted that there are currently no specific Australian guidelines for the management of APDS. Figure 2 shows the treatment algorithm including leniolisib

for symptomatic APDS in Australia, which was provided in the submission and the PSCR.

Figure 2: Treatment algorithm including leniolisib for symptomatic APDS in Australia



Source: Pre-Sub-Committee Response (PSCR)

4.6 Leniolisib acts by directly inhibiting the overactive PI3Kδ protein present in patients with APDS. By selectively inhibiting p110δ, the catalytic subunit of the PI3Kδ enzyme complex, and normalising PI3Kδ pathway activity in patients with APDS, leniolisib inhibits the recruitment and activation of a range of downstream messengers in the PI3Kδ signalling pathway. In turn, this diminishes the dysregulation of immune B and T cells and re-establishes their normal development and maturation.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated standard of care (SoC) as the main comparator. While SoC was likely a reasonable comparator to leniolisib, in clinical practice, leniolisib would be used in addition to SoC rather than completely replacing SoC; however, the utilisation of different components of SoC may differ depending on whether a patient also receives leniolisib. For example, use of mTOR inhibitors was not allowed in the clinical trial and concomitant use with leniolisib would not be allowed under the proposed restrictions.

5.2 SoC refers to a range of treatments which are currently used in Australia to manage symptoms of APDS. Following confirmed genetic diagnosis of APDS, treatment in Australia is tailored to the individual's presentation and needs, and may include immunoglobulin replacement therapy (IRT; including intravenous

(IVIg) and subcutaneous (SCIg) options), antimicrobial therapy (antibiotics, antifungal and antiviral drugs) and immunosuppressive therapy (e.g., corticosteroids, mammalian target of rapamycin (mTOR) inhibitors (predominantly sirolimus) and rituximab, which are all prescribed off-label for APDS).

5.3 The evaluation suggested sirolimus alone (instead of as part of SoC) should be considered the comparator to leniolisib, given that the APDS Case Series Report – Australia (2025) indicated that six of the seven (86%) patients who used leniolisib also used sirolimus, with only one patient treated with leniolisib without having been treated with sirolimus. However, there was no clinical evidence presented in the submission that would allow comparison of these treatments with leniolisib as sirolimus use was not permitted in Study 2201. The leniolisib submission to NICE included an indirect treatment comparison using a SoC arm comprised of patients from the ESID-APDS registry (see paragraph 6.48 for a description of this registry) that better represented current UK clinical management; however, a similar indirect treatment comparison was not presented in the submission. The PSCR argued that sirolimus should not be considered a stand-alone comparator for leniolisib given it has only been prescribed in a minority of patients globally and the utilisation of sirolimus is limited due to toxicities (including pulmonary toxicity), complex dosing in growing children with a frequent need for drug-level monitoring, and complications due to worsening immunodeficiency. The Sub-Committees noted that sirolimus would only be effective in treating some manifestations of APDS and agreed with the PSCR that it would not be used commonly in clinical practice in Australia and should not be considered a primary comparator for leniolisib.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented a clinical case study where treatment with two years of treatment with leniolisib resulted in improved lung function, fewer infections, and improved quality of life. The patient described treatment as "not a cure but feels close". The clinician discussed the natural history of the disease and described that leniolisib would be a game changing treatment for APDS in Australia as it corrects the root cause of APDS and manages infection.

6.2 The clinician addressed other matters in response to the Committee's questions. Regarding measuring response to treatment with leniolisib, the clinician noted that it is difficult to define appropriate response criteria that would apply to all patients since APDS is a rare disease there is considerable variation in the

manifestations experienced by patients and there are multiple health benefits that can be achieved and measured. In saying this, the clinician noted the most important overall aim of treatment is to slow down or prevent disease progression and maintain quality of life, particularly by preventing worsening of bronchiectasis. Therefore, a continuing criterion of stable or responding to treatment would be appropriate, particularly given this is a lifelong treatment. The clinician noted that the life-expectancy for patients with APDS is difficult to define as the condition has only been characterised in the last 10 years. Additionally, the clinician noted it is likely that uptake of leniolisib will be high if leniolisib was made available on the PBS. The PBAC considered the clinician's responses to the Committee's questions were informative to the restrictions and estimates for uptake for leniolisib.

Consumer comments

6.3 The PBAC noted and welcomed the input from individuals (1), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described how debilitating and isolating APDS is given the frequency of infections resulting in limited participation at work and school. The input described the benefits of treatment with leniolisib including reduced frequency of illness which has resulted in avoiding stem cell or lung transplants and allowed the patient to leave the house. The patient described the increase in quality of life in terms of physical, emotional and mental health. The patient described the side effects of leniolisib, although hard to distinguish from infection, are manageable. The patient noted patients on leniolisib will also still need to be able to access plasma and antibiotics. The patient raised some barriers to accessing leniolisib noting that having access to home delivery of leniolisib was considered important given APDS can make leaving home difficult, and for those who have difficulty swallowing the oral form will be challenging. The patient also suggested that restrictions should not be too strict as to limit access for patients who would benefit from the treatment.

6.4 The PBAC welcomed the comments from the Australasian Society of Clinical Immunology and Allergy (ASCIA) and AusPIPs Inc (an advocacy group for people who have Primary Immune Deficiency (PID)). The input from health professionals and organisations noted how rare APDS is and that there are limited effective treatment options. The comments confirmed the current treatments for APDS are non-specific and generally include anti-microbial and immunosuppressive therapy, including IVIg/SCIg and prophylactic antibiotics. The comments noted that is has been shown in studies that leniolisib helps manage specific features of APDS which do not respond to other treatments, such as cytopenias, and has also been shown to reduce IVIg/SCIg requirements. The comments stated the benefits of leniolisib (including fewer infections, reduced hospitalisations and immunoglobulin infusions, increased quality of life and engagement with the

community without the fear of being immunocompromised) outweigh the side effects of treatment. AusPIPs Inc acknowledged that there is no guarantee that leniolisib will bring about a cure for APDS but leniolisib has the best clinical trial evidence for effectiveness in people with APDS.

6.5 The PBAC noted ASCIA stated that haematopoietic stem cell transplantation (HSCT) is not considered to be a suitable comparator to leniolisib. HSCT is an alternative non-drug therapy that has been described by Australian clinical experts as a 'potentially curative medically indicated rescue therapy' however is a high-risk procedure that is not an option for many APDS patients. Additionally, ASCIA noted that if an individual is tested because a family member (e.g. a child) had been symptomatic and diagnosed with APDS and the individual is assessed by an experienced clinician as asymptomatic, no treatment is required or provided.

6.6 The PBAC noted the comments were supportive of the evidence provided in the submission. The PBAC valued the comments provided as the input allowed insight into the patient and health care provider perspective for a rare disease.

Clinical studies and trials

6.7 The submission was primarily based on one phase 3 head-to-head randomised controlled trial (RCT) that compared leniolisib to placebo (as a proxy for SoC) in patients with APDS aged 12 to 75 years (Study 2201 Part II) and two associated non-randomised studies (Study 2201 Part I: a phase 2 single-arm within-patient, dose-escalation trial and Study 2201E1: an open-label extension study).

6.8 Additionally, the submission identified one study (Whalen 2025) and four *post hoc* analyses utilising data from Study 2201 Part II and Study 2201E1 that were included in the submission. The Sub-Committees noted that the submission relied on many post-hoc analyses (internal documents and unpublished manuscripts) in an attempt to fill the gaps in published data. These analyses were associated with a high risk of bias.

6.9 Details of the trial and studies presented in the submission are provided in Table 2.

Table 2: Trial/studies and associated reports presented in the submission

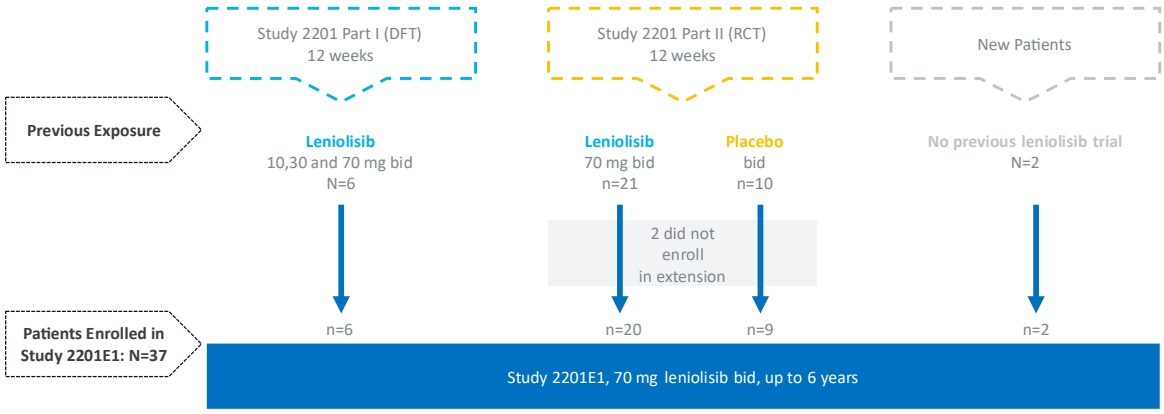
Trial ID	Protocol title/ Publication title	Publication citation
CCDZ173X2201 Part I [NCT02435173]	Effective "activated PI3Kδ syndrome"-targeted therapy with the PI3Kδ inhibitor leniolisib. Successful Clinical Study of Leniolisib (CDZ173), a Small Molecule PI3K-Delta Inhibitor, in Patients with APDS/PASLI.	Rao VK et al., Blood. 2017 Nov 23;130(21):2307-2316. doi: 10.1182/blood-2017-08-801191 Rao VK, et al. Journal of Clinical Immunology. 2017 Feb 1;37(2):204.
CCDZ173X2201 Part II [NCT02435173]	A randomised, placebo-controlled, phase III trial of leniolisib in activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS): Adolescent and adult subgroup analysis. A randomized, placebo-controlled phase 3 trial of the	Rao VK et al., Clin Immunol. 2025 Jan; 270:110400. doi: 10.1016/j.clim.2024.110400 Rao VK et al., Blood. 2023 Mar

Trial ID	Protocol title/ Publication title	Publication citation
	PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome.	2;141(9):971-983. doi: 10.1182/blood.2022018546
	Immunological and Exploratory Outcomes from a Phase 3, Placebo-Controlled, Randomized Clinical Trial of PI3K Delta Inhibitor Leniolisib in Patients with Activated PI3K Delta Syndrome (APDS/PASLI).	Rao VK, et al. European Journal of Allergy and Clinical Immunology. 2023 Mar 12;78(S111):39–55.
	Primary and safety outcomes of a phase 3 placebo controlled, randomized clinical trial of PI3K. (2022).	Rao VK et al., Allergy and Asthma Proceedings, 43(6), 560–567. https://doi.org/10.2500/aap.2022.43.220064
	Phase 3 Placebo-Controlled, Randomized Clinical Trial Outcomes of PI3K Delta Inhibitor Leniolisib in Patients with Activated PI3K Delta Syndrome (APDS/PASLI).	Rao VK, et al. 2022. Journal of Clinical Immunology. 42(S1):S1–S115.
CCDZ173X2201E1 [NCT02859727]	Long-term treatment with selective PI3Kδ inhibitor leniolisib in adults with activated PI3Kδ syndrome.	Rao VK et al,, Blood Adv. 2024 Jun 25;8(12):3092-3108. doi: 10.1182/bloodadvances.2023011000
	Interim Analysis: Open-Label Extension Study of Leniolisib for Patients with APDS.	Rao VK et al., Journal of Allergy and Clinical Immunology, 2024; 153(1), 265-274.e9. https://doi.org/10.1016/j.jaci.2023.09.032
	Interim Analysis of Safety and Hematological Parameters of an Ongoing Long-Term Open-Label Extension Study of Investigational PI3Kδ Inhibitor Leniolisib for Patients with Activated PI3K Delta Syndrome (APDS) through December 2021.	Rao VK et al., Blood 2022; 140 (Supplement 1): 1643–1645. doi: https://doi.org/10.1182/blood-2022-160334
	Safety and Efficacy of Long Term Suppression of PI3Kinase Pathway By Small Molecule PI3K-Delta Inhibitor, Leniolisib in Apds (Activated PI3Kδ Syndrome).	Rao VK et al., Blood 2018; 132 (Supplement 1): 3706. doi: https://doi.org/10.1182/blood-2018-99-113426
Whalen 2025 (Study compares data from Study 2201E1 and the ESID-APDS registry)	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.	Whalen J et al., Clinical and Experimental Immunology, Volume 219, Issue 1, January 2025, https://doi.org/10.1093/cei/uxae107.
Post hoc analysis Study 2201 Part II and 2201E1	Sponsor internal document.	Data file provided with submission titled "Pharming – *Post Hoc* Analysis of Study 2201 and 2201E1"[a]
	Leniolisib Effect On Response Rates For Select Outcomes In Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS).	Harrington A et al. Annals of Allergy, Asthma & Immunology, Volume 133, Issue 6, Supplement, 2024, Page S60. https://doi.org/10.1016/j.anai.2024.08.201
Post hoc analysis: Study 2201 Part II and 2201E1	Sponsor internal document.	Data file provided with submission titled "Pharming – 2024 – Pharming Data on File. Combined responder analysis [a]
Supplementary Analysis IA2	Sponsor internal document.	Not published
Post hoc analysis Study 2201 Part II and 2201E1	Unpublished manuscript: Rao et al. Short-Term Changes in Disease Activity May Predict Long-Term Clinical Outcomes in Activated Phosphoinositide 3-Kinase Delta Syndrome. Dated 6 March 2025.	Data file provided with submission titled "Rao et al. - Short-Term Changes in Disease Activity May Predict"

ADPS = activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome; ESID = European Society for Immunodeficiencies; PASLI = p110δ-activating mutation causing senescent T cells, lymphadenopathy and Immunodeficiency
[a] These documents included only data tables and did not appear to contain any analysis text. It is unclear if they have been published.
Source: Tables 2.3, 2.4 and 2.5, pp73-78 of the submission.

6.10 Figure 3 provides a visual summary of the series of three Study 2201 trials/studies (Study 2201 Part I, Study 2201 Part II and Study 2201E1, the extension phase of Study 2201) which provided the primary clinical evidence.

Figure 3: Visual summary of treatment details for the trial/studies within Study 2201



Source: Figure 2.1, p92 of the submission

6.11 The key features of the direct randomised trial, studies and other included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial/study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Study 2201 Part I	6	Phase II, OL, MC, non-randomised, dose-finding, dose escalations study; 12 weeks	High	Patients with APDS aged 12–75 years old	- Safety; - SF-36
Study 2201 Part II	31	R, OL, DB, MC, placebo-controlled study; 12 weeks	Low	Patients with APDS aged 12–75 years old	- % naïve B cells; - Lymphadenopathy; - Lymphoproliferation and splenomegaly; - Safety; - SF-36
Study 2201E1	37	Phase II, OL, MC, non-randomised; up to 6 years	High	Patients with APDS aged 12–75 years old	- Safety; - % naïve B cells; - Lymphoproliferation; - Infection frequency; - SF-36
Whalen 2025	99[a]	Comparison of patients in Study 2201E1 (leniolisib arm) and the ESID-APDS registry (control arm)	High	Study 2201E1 and the ESID-APDS registry	- Change in serum IgM levels; - Respiratory infections;
Post hoc analysis A	39	*Post hoc* study assessing 'response rate', where a responder was a patient whose change from baseline exceeded the median MCID estimation reported from a Delphi panel.	High	Study 2201 Part II and Study 2201E1	Responders for improvement in lymph node size, spleen volume, % of naïve to total B-cell ratio, haemoglobin, platelets and lymphocytes.
Post hoc analysis B	39	*Post hoc* study assessing 'response rate', where a responder was a patient whose change from baseline exceeded the median MCID estimation reported from a Delphi panel.	High	Study 2201 Part II and Study 2201E1	Responders for improvement in lymphoproliferation and cytopenia.
Supplementary analysis IA2	39	*Post hoc* study assessing 'response rate'.[b]	High	Study 2201 Parts I and II and Study 2201E1	Responders for SF-36 subscales. [b]
Tutein Nolthenius 2025 (unpublished manuscript)	39	*Post hoc* study comparing Study 2201E1 (leniolisib population) vs the APDS-ESID registry (SoC population)	High	Study 2201E1 and the ESID-APDS registry	Associations between short-term disease activity endpoints and longer-term clinical outcomes.

APDS = activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome; DB = double blind; ESID = European Society for Immunodeficiencies; Ig = immunoglobulin; MC = multi-centre; MCID = minimal clinically important difference; OL = open label; R = randomised.

[a] Whalen 2025 included all 37 patients from Study 2201E1 (leniolisib arm) and 62 and 49 patients from the ESID-APDS Registry (control arm) for analysis of respiratory tract infections and serum IgM levels, respectively.

[b] Further details were unclear as details were not provided in submission.

Source: Section 2.4 of the submission.

6.12 The risk of bias in Study 2201 Part I and 2201E1 were considered to be high due to risk of bias from measurement of the outcome because all patients were known to have received leniolisib and there is potential for a higher risk of bias regarding the generalisability of patients to the wider APDS population due to the small number patients enrolled in the studies. The risk of bias of Whalen 2025 was

considered high as there was potential risk of bias in selection of participants into the study and in measurement of the outcome because the study compared data from two different studies (Study 2201E1 and the ESID-APDS registry). The risk of bias for all the included post hoc analyses was considered high. These studies may be associated with numerous types of bias due to confounding, selection of participants into the study, missing data and the selection of the reported results.

6.13 Post hoc analyses A and B were responder analyses based on response thresholds derived from a Delphi panel with 24 clinicians with experience in managing patients with APDS or primary immunodeficiency disorder (PID) in Europe or the US. 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 that "you would consider clinically meaningful" or "the smallest improvement on each outcome that you would consider to be meaningful or important", i.e. a minimum clinically important difference (MICD). These MCID estimations were then used to assess the results of Study 2201 Part II and Study 2201E1 to determine the proportion of patients who were considered to be responders for each outcome.

6.14 The submission relied on a wide range of clinical inputs in the economic model. However, not all of them were reported directly in the included studies and required further manipulation of the data and as such, were not discussed under comparative effectiveness or comparative harms but instead will be discussed under the economic analysis section below. These outcomes include:

- Manifestation rates for lymphoproliferation, gastrointestinal manifestations, cytopenia, infections, malignancies, bronchiectasis-associated airway disease, advanced lung disease and hearing loss;
- Treatment discontinuation rates; and
- Mortality.

Comparative effectiveness

6.15 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 (Table 4). While the results indicate that leniolisib treatment resulted in a significant increase in naïve B cells as a percentage of total B cells, this analysis was underpowered due to the inclusion of fewer patients than anticipated. Consequently, the magnitude of these results should be interpreted with caution.

Table 4: Naïve B cells as a % of total B cells, change from baseline at Day 85 (Week 12), Study 2201 Part II

	Adjusted mean CfB (SE)a	Comparison of adjusted means			
		Difference	SE	95% CI	2-sided p-value
Primary efficacy analysis (B-PD analysis set)[b] – co-primary endpoint					
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) [c]					
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)				

bid: twice daily; CfB: change from baseline; CI: confidence interval; PD: pharmacodynamics; SE: standard error.
[a] 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.
[b] Only included patients in the PD analysis set with fewer than 48% naïve B cells out of total B cells at baseline. Comparatively, a total of 31 patients (21 randomised to leniolisib and 10 randomised to placebo) were enrolled in Study 2201 Part II.
[c] 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.
Source: Table 2.19, p109 of the submission.

6.16 Post hoc analysis A reported that 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 (Table 5). The responder analysis was based on the results of the Delphi panel, that estimated that after three months of treatment, an increase of ≥20% from baseline in percentage of naïve B cells out of total B cells in adults with APDS would be considered clinically meaningful.

Table 5: Post hoc analysis A: Post hoc 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)
Patients 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 patients contributing to the analysis[a]	12	5
Number of responders (%)	12 (100%)	0 (0%)
RD (95% CI)	1.00 (0.48, 1.00)	
P value[b]	p<0.001	
All patients		
Responder analysis of participants with ≥20% increase from baseline to day 85 in the percentage of naive to total B cells		
Number of patients contributing to the analysis[c]	17	8
Number of responders (%)	16 (94%)	1 (13%)
RD (95% CI)	0.82 (0.42, 0.97)	
P value[b]	p<0.001	

CI = confidence interval; RD = risk difference.
[a] For patients without data at Day 85, the closest visit day prior to day 85 was used. Consequently, for the leniolisib arm, day 85 data was used for 8 patients and day 57 data was used for 4 patients. Day 85 data was available for all placebo patients.
[b] Data were analysed using the Fisher's Exact Test.
[c] For patients without data at Day 85, the closest visit day prior to day 85 was used. Consequently, for the leniolisib arm, day 85 data was used for 13 patients and day 57 data was used for 4 patients. Day 85 data was available for all placebo patients.
Source: Table 2.20, p111 of the submission.

6.17 The responder analysis for increase in percentage of naïve B cells (where patients with ≥20% increase from baseline in percentage of naïve to total B cells at week 12 were classified as responders) included only 17 patients in the leniolisib arm (out of 21 enrolled) and eight patients in the placebo arm (out of 10 enrolled). It was unclear why this analysis did not include all randomised patients, and no details were provided with the submission to explain their exclusion. The responder analysis for participants with <48% naive to total B cells at baseline was also associated with a higher degree of uncertainty due to smaller patient numbers. Nonetheless, the number of patients classified as responders was substantially greater in patients treated with leniolisib compared to placebo regardless of which patient population was considered, though the analyses were likely associated with high uncertainty due to small patient numbers and short follow-up.

6.18 Improvement in naïve B cells with longer-term treatment beyond Week 12 was informed by Study 2201E1. In Study 2201E1, at baseline, the mean percentage (SD) of naïve B cells was 58.16% (20.922; n=5). The percentage of naïve B cells increased at each timepoint throughout the extension study with a mean (SD) change from baseline of 23.58% (16.177) at Extension Day 84 (n=5) and 32.42% (25.293) at Extension Day 252 (n=5). However, given the small sample size, the lack of a comparator arm and still relatively limited duration (252 days of extension plus 85 days of Study 2201 resulted in less than one year of follow-up), the sustainability of immunophenotype normalisation using the mean percentage of naïve B cell to total B cells as a surrogate remains uncertain. It was unclear why data were only available for five out of the 37 patients enrolled in Study 2201E.

6.19 Tutein Nolthenius 2025 (unpublished manuscript) presented a post hoc study that included investigation of pairwise associations between six disease activity surrogate endpoints (serum immunoglobulin M (IgM) levels, naïve B cells as a percentage of total B cells, transitional B cells as a percentage of total B cells, senescent CD8+ T cells as a percentage of total CD8+ T cells, index lymph node size and spleen volume) and four clinical outcomes (patient global assessment (PtGA), Short Form 36 (SF-36): Physical component summary (PCS), SF-36: Mental component summary (MCS) and infection rate). There were no significant effects found between the surrogate end points (including naïve B cells) and infection rates when assessing short term change in the surrogate (change from baseline to day 85) with one year of follow-up. However, a statistically significant association between an increase in proportion of naïve B cells out of total B cells and a lower annualised infection rate ($p<0.001$, negative binomial modelling) was identified when change from baseline to day 506 visit was considered; with an increase of 1 percentage point in the proportion of naïve B cells associated with a 2.3% reduction in yearly infection rates.

6.20 The Sub-Committees considered given the lack of significance for the change from baseline to day 85 result and the post hoc nature of this analysis, the results should be considered highly uncertain and subject to a very high risk of bias from repeated analyses without any statistical consideration in a pre-defined statistical analysis plan.

6.21 The PBAC Guidelines v5.0 (Appendix 5) request biological reasoning concerning how the disease pathogenesis (for APDS) relates to the proposed surrogate measures and the target clinical outcome, independent of medicine actions. Such a biological reasoning was not provided in the submission. However, the following was provided in the sponsor's technical report accompanying the submission:

"A hyperactive PI3K pathway prevents normal B and T cell development, resulting in the clinical phenotype [observed for APDS]; the biological plausibility of this relationship has already been described, providing "Level 3" evidence of a relationship between the surrogate markers and [patient-centred outcomes] PCOs under the [European Network for Health Technology Assessment] EUnetHTA Surrogate Endpoints guidance. However, the possibility of generating "Level 2" evidence quantifying the strength of association between surrogate and PCO endpoints has not been explored."

6.22 Overall, the Sub-Committees considered that the surrogate outcomes, such as immune cell changes, provide a representation of the underlying disease activity for APDS, making them valid and meaningful outcomes. However, the Sub-Committees considered that the measured outcomes do not necessarily correlate well with clinical manifestation of the disease, and the submission and the PSCR did not provide strong quantitative evidence linking surrogate outcomes to final outcomes.

6.23 In Study 2201 Part II, the co-primary efficacy endpoint related to lymphoproliferation was met, with leniolisib treatment resulting in a statistically significant decrease in lymphadenopathy, as measured by the change from baseline 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 (Table 6). The effect in the primary analysis was consistent with the supportive analysis which used the sum of the square root of the products of diameters of index lesions to measure index lesion size.

Table 6: Index lesion size, 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] PD analysis set					
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)				

bid = twice daily; CI = confidence interval; PD = pharmacodynamics; SE = standard error of the mean; SPD = sum of product diameters.
[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.
Source: Table 2.21, p117 of the submission.

6.24 In Study 2201E1, effects of leniolisib treatment on index lesion size were sustained to Day 168 and Day 252. Tutein Nolthenius 2025 (unpublished manuscript) reported that a single timepoint analysis found a weak correlation between index lymph node size and PtGA at day 85 (r=-0.36; p=0.034*).* The PSCR stated that lymphadenopathy measures provide direct clinical utility, as pulmonary or gastrointestinal lymphoproliferation can lead to serious local complications. The Sub-Committees considered it was plausible that a reduction in lymph node size would have an impact on QoL based on these complications.

6.25 Post hoc analysis A investigated responders for change in index lesion size results for Study 2201 Part II (Table 7). The submission reported that the Delphi panel found a median reduction in lymph node size of ≥20% in adults and ≥25% in adolescents with APDS after three months of treatment would be considered clinically meaningful, therefore a responder was defined as any patient who achieved a reduction in lymph node of ≥20% (if adult) or ≥25% (if adolescent) at day 85 (week 12).

Table 7: Post hoc analysis A: 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)
Number of patients contributing to the analysis[a]	19	8
Number of responders (%)	17 (89%)	2 (25%)
RD (95% CI)	0.64 (0.16, 0.89)	
P value[b]	p=0.002	

[a] All patients had data at Day 85.
[b] Data were analysed using the Fisher's Exact Test.
Abbreviations: CI: confidence interval; RD: risk difference; SPD: sum of product diameters.
Source: Table 2.22, p119 of the submission.

6.26 The submission reported that the Delphi panel 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. In Study 2201E, at Day 252 or Day 168, 24 out of 30 patients (80%) reached these responder thresholds. (For patients without data at Day 252, data from Day 168 were used; Day 168 data were used for 18 patients and Day 252 data were used for 12 patients.) The proportion of responders at Day 252/168 of Study 2201E1 (80%) was lower than the proportion of responders observed at Day 85 of Study 2201 Part II (89%), indicating that fewer patients may be continuing to respond over time. As observed for the change in percentage of naïve B cells, the responder analysis for change in lymph node size included fewer patients than the total enrolled in Study 2201 Part II. Consequently, the analyses were potentially associated with a higher level of uncertainty regarding the incremental benefit for leniolisib. This issue was consistently present in all of the responder analyses presented in the submission, which are therefore all likely to be associated with a high risk of bias, and p-values from post hoc analyses should be interpreted with caution.

6.27 In Study 2201 Part II, change in the 3D volume and bi-dimensional size of the spleen, was assessed as a secondary endpoint. Reductions in splenomegaly were reported with leniolisib treatment at Week 12, as shown in Table 8.

Table 8: 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)[a]	−26.68 (12.14)	−1.37 (24.24)
Spleen bi-dimensional size (mm^2)[a]	−12.05 (12.75)	+6.22 (21.98)

Bid = twice daily; CfB = change from baseline; PD = pharmacodynamics; SD = standard deviation.

[a] 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).

Source: Table 2.22, p120 of the submission.

6.28 The submission reported that the Delphi panel 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. Post hoc analysis A reported that a significantly larger proportion of participants in the leniolisib arm achieved the nominated responder threshold compared to the placebo arm (Table 9).

Table 9: Post hoc analysis A: 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)[a]

	Leniolisib (n=21)	Placebo (n=10)
Number of patients contributing to the analysis	15	4
Number of responders (%)[b]	11 (73%)	0 (0%)
RD (95% CI)	0.73 (0.04, 0.93)	
P value[c]	p=0.018	

[a] This analysis would be associated with a high risk of bias due to the decreased number of patients included in the responder analysis.
[b] All patients had data at Day 85.
[c] Data were analysed using the Fisher's Exact Test.
CI = confidence interval; RD = risk difference.
Source: Table 2.25, p121 of the submission.

6.29 Post hoc analysis B reported that of the 19/31 patients from Study 2201 Part II who were analysed, all patients with enlarged lymph nodes and enlarged spleen at baseline randomised to leniolisib (15/15) were classified as responders, compared to no patients (0/4) randomised to placebo (Table 10). However, it was unclear if patients were required to achieve one or both responses (i.e. reduction in either lymph nodes and/or spleen) to be considered a responder. At Day 168 or Day 252 Study 2201E1, 23/24 (96%) of patients with enlarged lymph nodes and spleen at baseline were considered to have responded to leniolisib. (Day 168 data were available for 15 patients and Day 252 data were available for 9 patients.)

Table 10: Post hoc analysis B: 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)[a]

	Leniolisib (n=21)	Placebo (n=10)
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)	

CI = confidence interval; RD = risk difference.
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] This analysis would be associated with a high risk of bias due to the decreased number of patients included in the responder analysis.
Source: Table 2.27, p122 of the submission.

6.30 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 patients in the placebo arm (where four patients were reported to have anaemia at baseline). Furthermore, all four cases of thrombocytopenia reported at baseline in patients receiving leniolisib treatment were resolved at Day 85, whereas a patient in the placebo group continued to be affected with thrombocytopenia at Day 85.

6.31 The submission reported that the Delphi panel 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. At Day 85, 83% of patients achieved a response when receiving leniolisib, compared

to 50% in the placebo group although this difference was not statistically significant (Table 11).

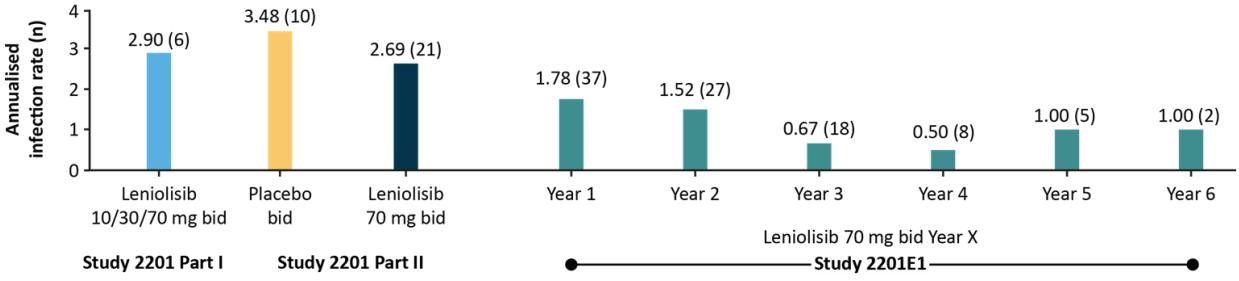
Table 11: Post hoc analysis B: Combined responder analysis of patients with reductions from baseline at Day 85 for haemoglobin, platelets and lymphocytes (Study 2201 Part II; PD analysis set)[a]

	Leniolisib (N = 21)	Placebo (N = 10)
Number of patients contributing to the analysis	12	4
Number of responders (%)	10 (83%)	2 (50%)
RD (95% CI)	0.33 (-0.19, 0.81)	
P value[b]	p=0.245	

Footnote: Patients 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] This analysis would be associated with a high risk of bias due to the decreased number of patients included in the responder analysis.
[b] Data were analysed using the Fisher's Exact Test.
Source: Table 2.29, p125 of the submission.

6.32 In Study 2201 Part II, annualised infection rates were lower in patients treated with leniolisib compared to the placebo group (2.690 versus 3.476 infections per year; Figure 4). For Study 2201E1, the submission claimed that a nominally significant decrease in annualised infection rate of 25% was reported with each additional year of leniolisib treatment (one-sided p=0.0256, data unverified). The submission claimed that these results demonstrate that long-term treatment with leniolisib leads to a sustained reduction in infections. It was unclear whether a claim based on an open label single arm extension study with no comparator arm, with an arbitrary reduction rate (25% annually) that was conducted post hoc was well supported.

Figure 4: Bar chart of annualised infection rates observed in Study 2201 Parts I and II, and Study 2201E1 (safety analysis set)



Bid = twice daily; OLE = open label extension.
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. Patients have completed the full time period if they were included in the analysis. For example, a patient with 360 days follow-up in Study 2201E1 does not contribute data to the 'Year 1' column. A patient with 380 days follow-up in Study 2201E1 contributes to 'Year 1' but not 'Year 2'.
Source: Figure 2.12, p126 of the submission.

6.33 While numerical increases were shown in all SF-36 scales in the leniolisib arm of Study 2201 Parts I and II, the change from baseline 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).

6.34 In Study 2201E1, mean SF-36 scores generally showed an improvement (increase) from baseline for all scales, however, the submission reported that the mean scores were generally still slightly below the average range for the general population.

Comparative harms

6.35 There were relatively few patients available for safety analysis due to the extreme rarity of APDS and as such, it was unclear if any report of no difference in adverse event (AE) rates reported was a reflection of actual lack of difference or a reflection of the small sample size. The majority of patients have received leniolisib for between 84-156 weeks in Study 2201E1, however there was only 12 weeks of controlled exposure providing comparative adverse event rates to placebo. Table 12 presents an overview of the AE data from all three Study 2201 studies/trials.

Table 12: Overall incidence for AEs across Study 2201 Parts I and II, and Study 2201E1 (safety analysis set)

	Study 2201 Part I			Study 2201 Part II			Study 2201E1 N=37 nE, nS (%)	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 (%)	RR (95% CI)[d]		
Patients with AEs	4, 2 (33.3)	3, 2 (33.3)	11, 4 (66.7)	92, 18 (85.7)	46, 9 (90.0)	0.95 (0.73,1.25)	418, 34 (91.9)	528, 36 (94.7)
Rates per participant-year[a]: AEs	8.9	6.5	22.1	18.0	17.9	NC	3.6	4.2
Study drug-related AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	6, 5 (23.8)	8, 3 (30.0)	0.79 (0.23,2.68)	7, 5 (13.5)	13, 9 (23.7)
Serious AEs[b]	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	5, 3 (14.3)	6, 2 (20.0)	0.71 (0.14,3.62)	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)	0, 0 (0.0)	NC	1, 1 (2.7)	1, 1 (2.6)
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)	NC	2, 2 (5.4)	2, 2 (5.3)
Grade 1 AEs	1, 1 (16.7)	2, 1 (16.7)	9, 3 (50.0)	65, 15 (71.4)	27, 8 (80.0)	0.89 (0.59,1.35)	228, 32 (86.5)	305, 33 (86.8)
Grade 1 AEs, rate per patient year[a]	2.214	4.322	18.062	12.723	10.514	NC	1.975	2.436
Grade 2 AEs	2, 0 (0.0)	1, 1 (16.7)	2, 1 (16.7)	19, 9 (42.9)	13, 5 (50.0)	0.86 (0.39,1.89)	104, 24 (64.9)	128, 28 (73.7)
Grade 3 AEs	1, 1 (16.7)	0, 0 (0.0)	0, 0 (0.0)	3, 2 (9.5)	4, 3 (30.0)	0.32 (0.06,1.61)	45, 10 (27.0)	49, 11 (28.9)
Grade 4 AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	3, 2 (9.5)	1, 1 (10.0)	0.95 (0.10,9.30)	1, 1 (2.7)	4, 3 (7.9)
Grade 5 AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (10.0)	NC	1, 1 (2.7)	1, 1 (2.6)
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)	NC	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)	NC	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)	NC	0, 0 (0.0)	0, 0 (0.0)

AE = adverse event; bid = Bis In Die (twice daily); N = number of participants studied; NC = not calculable; nE = number of AE events in the category; nS = number of participants with at least one AE in the category; RR = relative risk; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

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.
[d] RR calculated based on the risk experiencing the AE per patient, based on the number of participants with at least one AE in the category. Data indicates that each patient could experience the AE multiple more than once.
Data in italics calculated during the evaluation.
Source: Tables 2.39 and 2.40, p143 and 147 of the submission

6.36 During Study 2201 Part I, there was one instance of hearing loss reported (considered not study drug-related). There were no new incidences of hearing loss reported during Study 2201 Part II (across both leniolisib and placebo groups) or Study 2201E1. The submission reported that all five clinicians surveyed in the sponsor-commissioned UK Expert Consultancy report either 'agreed' or 'somewhat agreed' that a reduction in otitis infections would lead to a reduction in incident cases of hearing loss in individuals with APDS. Hearing loss is an outcome considered in the economic evaluation (see paragraph 6.56).

6.37 Two cases of malignancy have been reported in Study 2201. One was a case of classical Hodgkin's lymphoma which led to treatment discontinuation. The other case was a suspected urothelial carcinoma reported at Day 1329, for which treatment was temporarily interrupted. The case was reported recovered/resolved after five months and the patient resumed leniolisib. Neither event was considered to be related to leniolisib, by the investigator. The rate of malignancy in Study 2201 was relied upon by the submission in the economic evaluation (see Table 15 and Table 16).

6.38 No deaths or discontinuation of leniolisib were reported across Study 2201 Parts I/II. In Study 2201E1 one patient (previous placebo) discontinued leniolisib treatment in Week 118 (Extension Day 826), due to a diagnosis of Hodgkin's disease (SAE), which was considered unrelated to the study drug. One death in a 22-year-old male due to cardiac arrest (Week 125) was reported in Study 2201E1, which was considered unrelated to the study drug. Another death was reported in a 44-year-old female who had completed treatment with placebo in Study 2201 Part II and died of pulmonary hypertension approximately 4.5 months after the last dose of study medication. Deaths from Study 2201 was relied upon by the submission in the economic evaluation (see paragraph 6.60).

6.39 The TGA Delegate (TGA Delegate's overview, 6 December 2024) found that there was very little on which to base an analysis of the safety of leniolisib. The Delegate considered it likely that long term treatment will lead to the emergence of rarer adverse events associated with PI3Kδ inhibition in some patients. However, the rate of these events will be difficult to quantify given the low number of patients

who will ever be exposed to leniolisib for APDS treatment and may only be known if leniolisib acquires a more common indication in the future. The Delegate, however, considered the safety of leniolisib to be acceptable in the context of APDS being an incurable, debilitating and life-threatening condition and noted that the alternative standard of care for APDS also has significant potential adverse treatment effects.

6.40 As leniolisib is to be added to SoC, it was reasonable to expect that more AEs would be experienced by patients receiving leniolisib. However, there could also be reduction in SoC related AEs if the usage of SoC decreases with leniolisib treatment. Moreover, as noted by the TGA, there was a lack of long-term safety data. Overall, the claim that leniolisib plus SoC was non-inferior to SoC should be considered uncertain. However, based on available evidence as presented in the submission, the incremental impact to safety for patients receiving leniolisib appears to be manageable.

Benefits/harms

6.41 A summary of the comparative benefits and harms for leniolisib versus SoC over the 12-week duration of Study 2201 Part II is presented in Table 13. The benefit and harms should be interpreted with caution due to the relatively short treatment duration (12-weeks) and small patient numbers.

Table 13: Summary of comparative benefits and harms for leniolisib and SoC, Study 2201 Part II

Outcome	Leniolisib n/N	SoC n/N	RR (95% CI)	Event rate/100 patients[a]		RD (95% CI)
				Leniolisib	SoC	
Benefits						
Responders, naïve B cells[b]	12/12	0/5	1.00 (1.00, 1.00)	100	0	1.00 (0.48,1.00)
Responders, reduction in lymph node[c]	17/19	2/8	3.58 (1.07, 12.00)	89	25	0.64 (0.16, 0.89)
Harms[d]						
	Leniolisib n/N	**SoC n/N**	**RR (95% CI)**	**Event rate/100 patients[a]**		**RD (95% CI)**
				Leniolisib	**SoC**	
Any adverse event	18/21	9/10	0.95 (0.73, 1.25)	86	90	-0.04 (-0.28, 1.96)
Serious adverse event	3/21	2/10	0.71 (0.14, 3.62)	14	20	-0.06 (-0.35, 0.23)

HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; SoC = standard of care

[a] Treatment duration = 12 weeks.

[b] A patient was considered a responder if they experienced a ≥20% increase in the percentage of naive to total B cells (co-primary endpoint of Study 2201 Part II).

[c] A patient was considered a responder if they experienced a with ≥20 (adults) or 25% (adolescents) reduction in index lesion sum product of diameters (co-primary endpoint of Study 2201 Part II).

[d] Due to very low patient numbers resulting in low counts for AEs, comparisons for individual AEs were not provided.

Source: Tables 2.20, 2.22, 2.39, pp 74,119, 143 of the submission.

6.42 On the basis of direct evidence presented by the submission, for every 100 patients treated with leniolisib in comparison with SoC, over 12 weeks of treatment:

- Approximately 100 additional patients would be considered responders for the proportion of naïve B cells as a percentage of total B cells;
- Approximately 64 additional patients would be considered responders for reduction in size of lymph node;
- Approximately 4 fewer patients would experience an adverse event; and
- Approximately 6 fewer patients would experience a serious adverse event.

Clinical claim

6.43 The submission described leniolisib as superior in terms of effectiveness compared with SoC and non-inferior in terms of safety compared to SoC.

6.44 The Sub-Committees agreed with the Commentary that the therapeutic conclusion presented in the submission was partially supported by the evidence presented in the submission because:

- Study 2201 Part II demonstrated that leniolisib improves a range of immunity markers compared to placebo over 12 weeks:
  - Leniolisib met both co-primary endpoints of Study 2201 Part II, with a statistically significant (p=0.0002) increase from baseline in naïve B cells as

a percentage of total B cells and a statistically significant difference in lymphadenopathy (change from baseline [CfB] in the log10 transformed SPD of the index lesions; leniolisib arm -47.8% vs placebo arm -4.5%; p=0.0006). However, for both the co-primary endpoints the analyses were underpowered due to the inclusion of fewer patients than anticipated. Consequently, these results should be interpreted with caution.

- The submission presented a series of post hoc responder analyses which found that in the B-PD population, all patients treated with leniolisib (12/12) had a clinically meaningful response in naive B cells, versus no patients receiving placebo (0/5) (p<0.001). The responder analysis for reduction in lymph node size reported that 89% (17/19) of patients randomised to leniolisib versus 25% (2/8) randomised to placebo had a clinically meaningful response (p<0.002). However, all of the responder analyses were associated with a high risk of bias because these analyses were post hoc and did not include all randomised patients, which was not explained in the submission.

- While the primary endpoints and most other endpoints measured in the studies represent surrogate markers, there were very limited data to support the association between an increase in percentage of naïve B cells out of total B cells with a lower annualised infection rate (p<0.001, negative binomial modelling). The Sub-Committees considered the surrogate outcomes, such as immune cell changes, provide a representation of the underlying disease activity for APDS, making them valid and meaningful outcomes. However, the Sub-Committees considered that the measured outcomes do not necessarily correlate well with clinical manifestation of the disease, and the submission and the PSCR did not provide strong quantitative evidence linking surrogate outcomes to final outcomes. The Sub-Committees also noted that the PSCR stated that lymphadenopathy measures provide direct clinical utility, as pulmonary or gastrointestinal lymphoproliferation can lead to serious local complications. The Sub-Committees considered it was plausible that a reduction in lymph node size would have an impact on QoL based on these complications.

6.45 The Sub-Committees agreed with the Commentary that the submission's claim of non-inferior safety may be uncertain due to the limited comparative safety data available for leniolisib. As leniolisib is to be added on to SoC, it was reasonable to expect that more AEs would be experienced by patients receiving leniolisib. However, there could also be reduction in SoC related AEs if the usage of SoC decreases with leniolisib treatment. Overall, the claim that leniolisib plus SoC was non-inferior to SoC should be considered uncertain. However, based on available evidence as presented in the submission, the incremental impact to safety for patients receiving leniolisib appears to be manageable.

6.46 The PBAC considered that the claim of superior comparative effectiveness over SoC was reasonable based on the available comparative data for Study 2201 Part

II. The PBAC considered the demonstrated improvements in surrogate outcomes, such as immune cell changes, provide a representation of the underlying disease activity for APDS, and are therefore likely to result in improvements in patient-relevant outcomes such as infections, lung disease, lymphadenopathy and risk of lymphoma.

6.47 The PBAC agreed with the Sub-Committees and considered that the claim of non-inferior comparative safety over SoC was uncertain as there are limited comparative data available. The PBAC noted the TGA Delegate considered it likely that long term treatment with leniolisib will lead to the emergence of rarer adverse events associated with PI3Kδ inhibition in some patients. However, based on available evidence as presented in the submission, the incremental impact to safety for patients receiving leniolisib appears to be manageable.

Economic analysis

6.48 The submission presented a cost-utility analysis (CUA) that compared leniolisib + SoC with SoC alone based on one direct randomised trial (Study 2201 Part II), with additional clinical data from Study 2201E, the leniolisib early access program (EAP) and the ESID-APDS registry. The ESID registry is a prospective, observational, international registry of patients with IEIs that includes a cohort of patients with a genetic confirmation of APDS (the ESID-APDS registry). Out of the 150 patients enrolled on the ESID registry, there were 140 patients enrolled on the ESID-APDS registry (mean patient age at last visit 19.1 years; mean follow up 2.6 years; 6 November 2023 data cut), with enrolment ongoing. The longitudinal nature of the ESID-APDS registry allows the collection of data for APDS manifestations, treatment utilisation and mortality over time.

6.49 The key components of the economic model are presented in Table 14.

Table 14: Summary of model structure, key inputs and rationale

Component	Description	Justification/comments
Comparison	Leniolisib with SoC, compared to SoC alone (SoC therapies include a range of therapies which are patient specific, dependent on particular manifestations and included immunosuppressive drugs including sirolimus and rituximab)	The Commentary considered this was generally reasonable.
Type of analysis	Cost-utility analysis (CUA)	Reasonable
Outcomes	• Mortality • Lymphoma and other malignancies • (Advanced) lung disease, decline in lung function and recurrent pneumonia leading to bronchiectasis-associated airway disease • Infections • Gastrointestinal symptoms (resembling IBD) • Hearing loss • Immune system function ○ Immunophenotype measures (lymphocyte counts, cytopenia, immunoglobulin levels,	As patients with APDS experience a wide range of manifestations, the Commentary considered this list of outcomes appears reasonable.

	cytokine and chemokine levels, use of IRT and antibiotics) ○ Lymph node size, spleen and liver volume size • Health-related quality of life (QALY)	
Time horizon	Lifetime	The model used a lifetime time horizon of 85 years (or until patients are 100 years old). However, Study 2201 Part II provided only 12 weeks of comparative data, therefore the robustness of using this data for the nominated time horizon was uncertain. Additionally, as data from the ESID-APDS registry reported that patients had a median survival age of 44 years, an 85-year time horizon may not be reasonable (Maccari, unpublished manuscript, November 2024 data set). The Sub-Committees considered the 85-year time horizon was not reasonable based on the short trial follow-up and life-expectancy of the population.
Methods used to generate results	Markov Cohort state transition model; partitioned manifestations	Reasonable
Health states	Three treatment-based health states: Alive on leniolisib; Alive and not on leniolisib; and Dead. Additionally, patients in the alive states experience APDS-related manifestations which the submission considered to be tunnel health states	In the treatment-based health states, the effectiveness of leniolisib was captured in a reduction in incidence, resolution, or reduction in severity of manifestations which subsequently improved HRQoL and reduced costs. The Sub-Committees noted that this structure was unusual and created some complexities.
Cycle length	Yearly	As only 12 weeks of comparative evidence was available for leniolisib, there were not sufficient data to reliably inform a full model cycle.
Transition probabilities	Transition from Alive on leniolisib to Alive and not on leniolisib based on a fixed assumed annual discontinuation rate informed by Study 2201E1 (May 2024 data cut). Patients who discontinue leniolisib revert to age-specific SoC level manifestation rates applicable at age of leniolisib initiation. Mortality is a function of: • For the SoC arm: ESID-APDS registry-based (in the base case) age-specific rates of APDS mortality, with associated KM-curve fitting and extrapolation; and • For the leniolisib arm: application of relative risks (RRs) to the general population mortality risk; RRs derived from observed mortality rates in Study 2201 and the EAP, compared with age-matched general population risks. Manifestation rates are calculated using: • For the SoC arm: ESID-APDS registry-based age-specific rates of APDS manifestations (base case), as well as subsequent	The Sub-Committees considered treatment continuation was difficult to extrapolate given the limited data available but using a fixed discontinuation rate may not be reasonable. The manifestation rates for leniolisib appear to be optimistic. For example, the hazard ratio for each of lymphoproliferation, gastrointestinal manifestations and cytopenia for leniolisib versus SoC was assumed to be 0 which were not based on direct comparative clinical evidence. Mortality was not linked to manifestations, which may not be reasonable given the seriousness of many of the manifestations seen in patients with APDS. No ESID-APDS Kaplan-Meier (KM) mortality data was used in the model and all the extrapolations were overestimated compared to the observed KM period. The Sub-Committees considered the use of different sources of mortality data for the treatment arms was problematic and introduced substantial

	extrapolation; and • For the leniolisib arm: results of Study 2201 Parts I and II, Study 2201E and the leniolisib EAP, used to generate hazard ratios which are applied to SoC manifestation rates.	uncertainty.
Discounting	5% per annum	The Commentary identified errors in the application of discounting but noted the incremental results remain the same and therefore this did not change the ICER.
Perspective	Healthcare system perspective	Appropriate
Software package	Excel	Appropriate

APDS = activated PI3Kδ syndrome; CUA = cost-utility analysis; EAG = external assessment group; EAP = early access program; ESID = European Society for Immunodeficiencies; IBD = Inflammatory bowel disease; IRT = immunoglobulin replacement therapy; KM = Kaplan Meier; NICE = National Institute for Health and Care Excellence; QALY = quality adjusted life year; RR = relative risk; SoC = standard of care

[a] NICE. Final draft guidance – leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over [ID6130]. Issue date March 2025.

Source: Table 3.1, pp159-160 of the submission.

6.50 Patients in the leniolisib arm enter the model on-treatment ('alive on leniolisib' health state) and could either discontinue treatment ('alive and off leniolisib' health state) or die ('death' as an absorbing state). Within the 'alive on leniolisib' and 'alive off leniolisib' health states there were 20 tunnel states that modelled different manifestation incidences and survival rates post-discontinuation (i.e. patients assumed to have manifestations are assumed to never improve and will remain in the specific manifestation state until death due to the application of a cumulative probability of manifestation rather than a transition probability). The Sub-Committees noted that the submission argued that this unusual structure was justified on the basis that a Markov cohort approach would need to capture the numerous potential combinations of manifestations, which would be complex to implement and would rely on transition probabilities from a limited population base. The Sub-Committees noted these arguments but also considered that several assumptions adopted in this approach (e.g. assumptions underpinning transitions) appeared optimistic. The Sub-Committees considered that the assumption that manifestations never improved was reasonable for some (e.g. hearing loss) but was not reasonable for others (e.g. infections).

6.51 The benefits of leniolisib were modelled by the resolution or reduced incidence and severity of manifestations and SoC treatment use. However, patients who were initiated on leniolisib but discontinued are assumed to have the manifestation rate of a patient treated with SoC aged 15 years at the first cycle after discontinuation irrespective of the patient's age when they discontinued treatment, and then accumulating higher manifestation risks progressively (i.e. two years after discontinuation, they will have the manifestation rate of a patient treated with SoC aged 16 years). The Sub-Committees noted that this aspect of the model structure was not well-justified and the assumption that the risk of manifestations reverting to the starting age highly favoured leniolisib.

6.52 The time horizon in the model base case is 85 years, corresponding to patients being 100 years old at the end of the model based on a starting age of 15 years. However, the pivotal RCT (Study 2201 Part II) provided only 12 weeks of comparative evidence between leniolisib and SoC. Consequently, the available comparative data do not inform even a full (annual) cycle of the model and the extrapolation of these data to 85 years was highly uncertain. The Sub-Committees considered the time horizon used was optimistic, particularly given the limited duration of comparative data from the trial and the reduced life-expectancy of patients with APDS. Although the PSCR referred to "life-expectancy impacts" for leniolisib, the Sub-Committees noted that no impact on mortality was captured in the clinical trials and the trial captured surrogate outcomes only without any established correlation with mortality. Therefore, the Sub-Committees considered a shorter time horizon would be more acceptable.

6.53 Additionally, while the proposed leniolisib restriction would allow use in patients aged 12 years and older, the submission claimed that 15 years reflects the average age of the international APDS patient ESID-APDS registry. However, the Australian APDS Case Series Report, found the current median age of Australian patients to date is 25 years. The starting age had a moderate impact on the incremental cost effectiveness ratio (ICER); changing the start age to 12 years resulted in a [redacted]% increase in the ICER, and changing the starting age to 25 years decreased the ICER By [redacted]%.

6.54 Table 15 summarises the key health state events and sources of the transition probabilities for both treatment arms.

Table 15: Key health state event rates and transition probabilities

Event rate/transition probability	Description
SoC arm	
Manifestation rates	Patients experience age-specific rates of manifestations (lymphoproliferation, GI manifestations, cytopenias, malignancies, bronchiectasis and advanced lung disease) based on cumulative incidence reported in ESID-APDS registry data. Age-specific rates of hearing loss based on medical history data set of patients enrolled in Study 2201. Infection rate based on patients randomised to placebo in Study 2201 Part II.
Additional treatment rates	Patients were assumed to receive additional treatment with steroids, immunosuppressants, IRT, or undergo tonsillectomy (as a proxy for immune-related surgeries which may be carried out in APDS patients) or HSCT based on an age specific rate. These rates were informed by ESID-APDS registry data.
Mortality	Patients progress to death based on ESID-APDS registry.
Leniolisib arm	
Manifestation rates on leniolisib	Patients in the 'Alive on leniolisib' health state can experience manifestations but at reduced rates relative to SoC based on HR informed by Study 2201 part II, Study 2201E1 and assumptions. A proportion of patients were also assumed to experience manifestations of reduced severity when treated with leniolisib.
Additional treatment on leniolisib	Patients in the 'Alive on leniolisib' health state are assumed to use some additional treatments with corticosteroids (reduced rate with HR of 0.26, based on assumption only) and IRT (reduced rate compared to SoC, based on Study 2201 Part II and 2201E1) and assumed to have some tonsillectomy (38% reduction from SoC based on UK clinicians). Patients on leniolisib are assumed to have no use of immunosuppressants (appears to have been based on UK clinician opinion) or HSCT (assumption only).
Mortality on leniolisib	Calculated as an RR applied to the age-specific risk mortality of the general population.
Discontinuation	Patients discontinue leniolisib due to unplanned events (e.g. non-response, tolerability, patient choice) and revert to SoC only at a specified annual transition rate based on Study 2201E1 discontinuation data.
Post-discontinuation manifestation rates	In the first cycle post leniolisib discontinuation, leniolisib patients revert to SoC arm rates of manifestation incidence at baseline age of the model (i.e. 15 years of age in the base case), and each progressive year, will have the manifestation rate of the next year of age (i.e. two years/cycles after discontinuation, will have manifestation rate of SoC at age 16 years).
Post-discontinuation additional treatment	As for post discontinuation manifestation rates, post leniolisib discontinuation, leniolisib patients revert to SoC arm rates of additional treatment at the baseline age of the model (i.e. 15 years of age in the base case), and each progressive year, will have the additional treatment rate of the next year of age. It was unclear what this assumption was based on, as experts did not appear to have been asked on post-discontinuation treatment patterns.
Post-discontinuation mortality	Post leniolisib discontinuation, leniolisib patients revert to SoC arm rates of mortality which was based on ESID-APDS registry.

APDS = activated PI3K delta syndrome, ESID = European Society for Immunodeficiencies; HR = hazard ratio; HSCT = Hematopoietic stem cell transplantation; IRT = immunoglobulin replacement therapy; RR = relative risk; SoC = standard of care
Source: Table 3.11, p209 of the submission.

6.55 The manifestation rates for the leniolisib treatment arm were calculated as a function of the manifestation rates for the SoC arm. A hazard ratio (HR) was applied to each manifestation to reflect a reduction in the incidence of manifestations due to treatment with leniolisib. The submission assumed that for some manifestations, a proportion of patients in the leniolisib arm will resolve their manifestation at age 15 at the initiation of leniolisib. This led to an immediate decrease in manifestation rate at the start of the model for patients in the leniolisib arm compared to the SoC arm; for example, the cumulative proportion

of patients with lymphoproliferation in the leniolisib arm was 71.36% at age 14 but dropped to 2.93% at age 15 and remained at 2.93% for the duration of the model. In comparison, the cumulative proportion of patients with lymphoproliferation in the SoC arm was 71.36% at age 14, 73.15% at age 15 and continued to increase to a maximum of 93.95% at age 38 after which time it remained steady. Additionally, it was assumed that a proportion of patients in the leniolisib arm would have a reduction in symptom severity even if they have manifestations. The PSCR stated that NICE reported that for manifestation rates post leniolisib discontinuation, UK clinical experts found it was most clinically plausible for all manifestation incidence rates to return to pre-leniolisib treatment levels. However, the Sub-Committees considered it was uncertain if this assumption of ongoing benefit was justified given manifestations experienced by patients with APDS vary with age and patients initiating treatment are generally older than that was assumed in the model. The Sub-Committees noted the implication of this assumption was that the first year of therapy is more cost-effective relative to the later years. The Sub-Committees considered this was optimistic and unlikely to reflect outcomes for a chronic condition, requiring ongoing treatment.

6.56 Table 16 provides details of the HRs of manifestation rates as well as percentage resolution and severity reduction associated with leniolisib treatment applied in the model. The HRs, proportion with resolution of manifestation and severity reduction were primarily informed by the 2201E1 extension study or data from the EAP. However, the Sub-Committees noted the specific data sources and/or calculation of the HRs was often unclear and not all these values could be verified during the evaluation, and the reliability of some of these calculations appeared uncertain and based on some strong assumptions. For example, the HR for hearing loss of 0.33 was based on one reported AE of hearing loss in Study 2201 part I, which the submission then converted to an annualised rate of 0.0067 using all patients enrolled in Study 2201 (i.e. including part II and 2201E1) expressed as patient years, divided by an annual rate of 0.020 which was derived from a parametric fit to the medical history of patients in Study 2201. The Sub-Committees considered that the HRs applied to manifestations were highly uncertain due to small numbers of patients informing them and the limited documentation of sources. The Sub-Committee also noted large effect sizes both for immediate resolution and for ongoing HRs. Although the Sub-Committees considered assumptions of manifestation rates were structurally unavoidable, these assumptions introduced substantial uncertainty in the modelled costs and outcomes.

Table 16: Incidences, resolutions, and severity reductions for each manifestation given treatment with leniolisib

Manifestation	HR for incidence per year	% resolution of manifestation in the first year	% severity reduction
Lymphoproliferation	0.00[a]	96%	NA
Gastrointestinal manifestations	0.00[a]	36%	78%
Cytopenia	0.00[a]	78%	NA
Infections	1.00	0%	NA
Malignancies	0.41	0%	NA
Bronchiectasis-associated airway disease (excluding advanced lung disease)	0.28	10%	33%
Advanced lung disease	0.00	0%	100%
Hearing loss	0.33	0%	NA

HR = hazard ratio

[a] The incidence rates for lymphoproliferation, GI manifestations, cytopenia and advanced lung disease were assumed to be 0. i.e., the incidence of these manifestations was reduced by 100% compared to the SoC arm when patients received treatment with leniolisib.

Source: Manifestations sheet, PHG LENIOLISIB CUA MODEL FINAL.xlsm

6.57 Among the modelled reductions in manifestation rates, those with the highest impact on the ICER were:

- Lymphoproliferation (assumed HR = 1 and 0% resolution increased the ICER by %). The HR of 0 was based on there being no reports of persistent lymphoproliferation in Study 2201 Parts I and II, and Study 2201E1 (data cut-off May 2024) or the EAP survey. However, three incidences of non-persistent lymphadenopathy were reported in Study 2201, and it may therefore have been reasonable to assume that some patients receiving leniolisib would experience lymphoproliferation; and
- Gastrointestinal (GI) manifestations (assumed HR = 1 and 0% resolution increased the ICER by %). GI manifestation was not measured in Study 2201 and instead, non-comparative data from the EAP was used. It was unclear how a HR of 0 was derived as amongst all patients in the EAP survey with responses to GI questions (n=28), one patient with colitis at baseline experienced a new colitis event during treatment of leniolisib (>2 years).

6.58 Notably, the submission's model estimated the proportion with bronchiectasis-associated airways disease excluding advanced lung disease by subtracting the total proportion of advanced lung disease from the total proportion of bronchiectasis-associated airways disease at each cycle. However, the proportion of patients with bronchiectasis-associated airway disease excluding advanced lung disease was higher in the leniolisib arm than in the SoC arm due to the method of calculation as it was assumed that the proportion of patients with advanced lung disease was substantially lower in the leniolisib arm than in the SoC arm. It was unclear if this was plausible given the assumptions made by the submission that leniolisib treatment would result in lower rates of patients with bronchiectasis-associated airway disease.

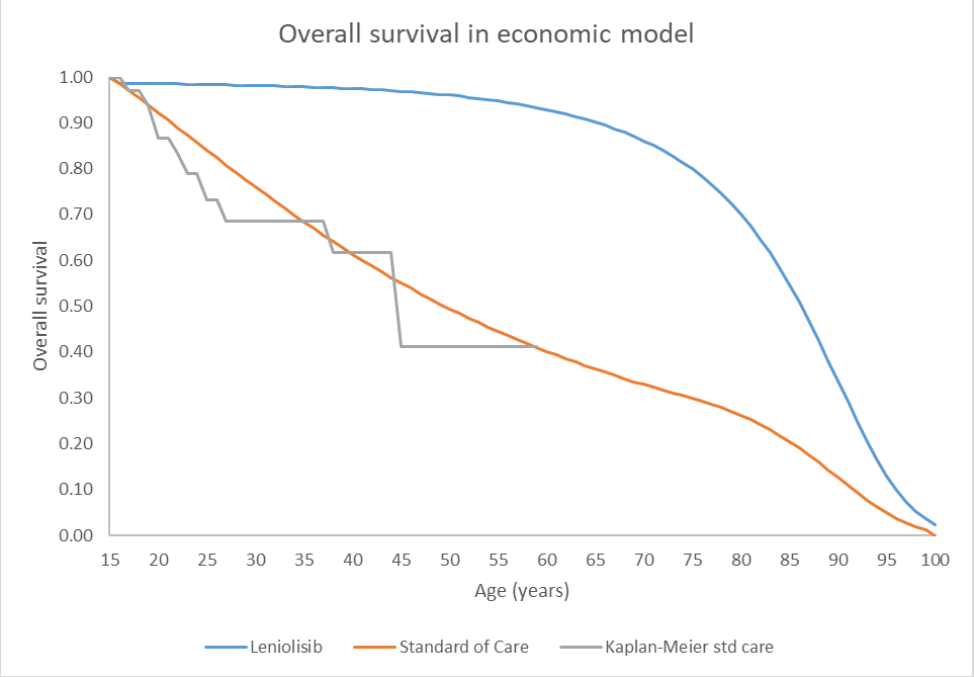
6.59 Leniolisib patients were assumed to discontinue treatment and transition to SoC over time in the economic model. A fixed rate of 2.55% was applied for the leniolisib discontinuation rate in the model. This was based on continued follow-up in Study 2201E (May 2024 data cut) and the leniolisib EAP (February 2025). During 313.7 patient-years of treatment, there have been eight discontinuations, giving an annual rate of 2.55%. However, as reiterated in the PSCR, this differed compared to the discontinuation rate of 2.7% that the NICE found was appropriate. Using a higher discontinuation rate results in a lower ICER (e.g. increasing the discontinuation rate to 5% per year decreases the ICER by %). This was likely due to the assumption that patients who discontinue leniolisib will have a manifestation rate equal to the rate at the first post discontinuation cycle (i.e. the rate when patients are 15 years old, see paragraph 6.51), and illustrates that the model was likely biased in favour of leniolisib. The Sub-Committees considered using a fixed discontinuation rate may not be reasonable given APDS is a chronic disease and requires ongoing treatment. However, the Sub-Committees acknowledged there may not be further data to support an alternative approach.

6.60 Survival data for leniolisib was based on combined data from both Study 2201E and the EAP, and was based on 142/146 patients over 1.7 years of follow up. The submission stated that 2/142 patients died over a median of 1.7 years of follow up (98.7% survival). The relative risk (RR) of death was estimated by comparing survival for patients treated with leniolisib with the age- and follow-up-matched general population survival in Australia. Across the entire age- and follow-up-matched population in Study 2201 and the EAP, the expected survival was 99.9% for the general population versus 98.7% survival observed in people treated with leniolisib. Based on these calculations, the survival of patients treated with leniolisib was assumed to be 98.7% of the general population survival rates which was based on Australian life tables. Comparatively, mortality on SoC was extrapolated from the ESID-APDS data. The Sub-Committees agreed with the Commentary that the application of a HR based on the deaths of two patients over 1.7 years does not provide a robust approach to estimating the mortality of patients with APDS, particularly as this method assumes that patients are returned to near normalised immune function following treatment with leniolisib, which may not be reasonable.

6.61 The modelled overall survival for leniolisib, SoC and the KM data from the ESID-APDS registry which was used to inform survival in the SoC arm is presented in Figure 5. The submission stated that mortality in the “alive off leniolisib” health state (i.e. patients in the SoC arm, including patients who discontinued leniolisib) was based on ESID-APDS registry (data cut-off 26th of November 2024; N=158). Patients in the SoC arm are subject to the probability of all-cause mortality as reported directly from the ESID-APDS registry. The SoC survival curve was

extrapolated using a log logistic parametric curve in the base case which was chosen based on visual and statistical fit. It may not be reasonable to use mortality data from these different data sources to compare leniolisib versus SoC and it may have been more reasonable to instead apply a HR to the ESID-APDS survival data to account for improved survival anticipated for patients treated with leniolisib. The model estimated a substantial survival gain from leniolisib compared to SoC over the lifetime time horizon (3.17 LY gained). This was highly uncertain given follow up in Study 22201E was only 1.7 years and there was no comparative survival data between leniolisib and SoC to inform a survival benefit. Assuming a lower RR of 0.90 increased the ICER by %, and a RR of 0.8 increased the ICER by %. The Sub-Committees considered the submission's approach of using two different sources for mortality was problematic and was likely to be highly optimistic. The Sub-Committees noted that the mortality gain modelled was not supported by the clinical data.

Figure 5 : Survival curves in leniolisib vs SoC



Source: "Survival" worksheet, PHG LENIOLISIB CUA MODEL FINAL.xlsm

6.62 SF-36 HRQoL data was collected in Study 2201. However the submission claimed that SF-36 data from the leniolisib clinical studies could not be used to inform HRQoL in the base case of the economic model because SF-36 did not appropriately capture QoL benefits of treatment in APDS; baseline values in the trials were biased because patients had some manifestations at baseline (e.g., lymphoproliferation); and SF-36 could not be stratified by manifestation. The Sub-Committees considered the claim that trial-based utility values could not be used was not well-supported, and use of these values could have been explored. Instead, the model used an age-adjusted baseline utility and then applied utility

decrements and disutility multipliers to account for manifestations as they are experienced. Baseline utility was based on general population and disutilities were based on the literature. However, two different sources were used for adolescents (Le 2021) and adults (Redwood 2024) which led to some potential applicability concerns.

6.63 The impact of leniolisib was modelled via reductions in the incidence and/or prevalence of these manifestations and treatment use, with subsequent changes to HRQoL. Patients potentially incur multiple manifestations (and their associated disutilities) in a given year and over time. As individuals experience various manifestations and receive associated treatments, manifestation-specific utility impacts are applied to the age-adjusted baseline utility values for each treatment arm as follows:

- The disutility decrement for transient manifestations (e.g. acute infections) and short-term treatments was calculated as the difference between the utility for patients with the specific manifestation or treatment and the age-adjusted general population utility, then adjusted for the duration of the manifestation or treatment; and
- The disutility from long-term manifestations (e.g., malignancy) or continuous treatment was calculated as a utility multiplier. The utility multiplier was calculated using the utility for patients with the specific manifestation or treatment divided by the age-adjusted general population utility. For example, a patient with GI manifestations (with no change in severity e.g. in the SoC arm) was assumed to have just 47% (utility multiplier of 0.47) of the utility of a patient with no GI manifestation (or with improved severity), all else being equal. These decrements came from a large list of different sources. The submission did not adequately explain any of these calculations or reasons for using particular data sources.

6.64 The utility inputs, and sources are further described in Table 17.

Table 17: Utility multiplier or decrements applied in economic model

Input description	Utility multiplier or decrement	Source
Gastrointestinal disorder utility multiplier	Disutility multiplier = 0.47	The multiplier was claimed to be 0.41 from Wilson and Lucas 2018 (abstract/poster presentation) which presented a cost-effectiveness study in patients with moderate to severe Crohn's disease who have previously failed tumour necrosis factor alpha inhibitors in the United Kingdom. [1] It was unclear whether Crohn's disease was a reasonable proxy for informing GI manifestation disutilities.
Cytopenia utility multiplier	Disutility multiplier = 0.88	The 0.75 was based on the mean adjusted EQ-5D score reported in immune thrombocytopenic purpura patients (n=1,002) from Snyder 2008 which was a cross-sectional, descriptive study comparing immune thrombocytopenic purpura patients' HRQoL to age and gender matched controls in the US. (The EQ-5D score for controls was 0.83.)

Input description	Utility multiplier or decrement	Source
Lymphoma utility multiplier	Utility decrement in first year = - 0.592 Disutility multiplier after first year = 0.80	Estimation of utility decrement in the first year = 0.278 – 0.87 (i.e., first year utility of 0.278 minus the general population utility of 0.87 at age 35 years) = -0.592. 0.278 was the baseline utility for an APDS patient having malignancies from the submission's EQ-5D study informed by clinical experts. It was unclear why two different disutilities were required and why a flat decrease was used in the first year rather than a multiplier, as used for all subsequent years. It was also unclear why the model used the general population age of 35 years for this calculation and then 61 years for subsequent years. The disutility multiplier after first year was based on the EQ-5D scores of all patients at baseline reported in Launonen 2021 (n=1,132), which was an open label RCT in previously untreated patients with diffuse large B-cell lymphoma (DLBCL).
Infections		
Moderate lower respiratory infections disutility	-0.003	Disutility value based on Global Burden of Disease Study 2019 for all infections. Assumed to occur in 26% of patients (leniolisib and SoC arms) and claimed to be sourced from Coulter 2017. [1]
Severe lower respiratory infections disutility	-0.009	Assumed to occur in 21% of patients and claimed to be sourced from Coulter 2017.
Moderate upper respiratory infections disutility	-0.003	Assumed to occur in 41% of patients and claimed to be sourced from Coulter 2017.
Herpes zoster disutility	-0.004	Assumed a occur in 12% of patients and claimed to be sourced from Coulter 2017.
Infections: weighted average disutility	-0.004	Disutility was based on a weighted average using a proportion of patients from Coulter 2017.
Bronchiectasis utility multiplier	0.81	Based on EQ-5D baseline scores in the control group (n=103) reported in Brockwell 2020 which was a RCT conducted in patients with bronchiectasis.
Advanced lung disease utility multiplier	0.71	Based on EQ-5D baseline scores in adolescents (16 years or older) with cystic fibrosis and chronic P. aeruginosa infection reported in Bradley 2013, which was a study that investigated the HRQoL and healthcare resource use in cystic fibrosis patients (N=94). This was informed by the sample of patients with severe pulmonary exacerbations (n=19) (no exacerbations = 0.85, n=60; and mild exacerbations = 0.79, n=15).
Hearing loss disutility	-0.03	Disutility was based on the weighted average of disutility of mild hearing loss (0.01) and moderate hearing loss (-0.027) from Global Burden of Disease Study 2019, assuming a 50% split. [1]
Splenomegaly utility multiplier	0.81	Based on the EQ-5D baseline score in patients with myelofibrosis (N=187) reported in Mesa 2021, which was an RCT in patients with myelofibrosis treated with fedratinib or placebo. It appeared that in the model it was assumed that myelofibrosis was representative of lymphoproliferation in APDS based on splenomegaly being a common symptom, however this was unclear in the submission. It was also unclear whether myelofibrosis provided a reasonable representation of lymphoproliferation.
IRT		
SCIG disutility	0.00	Decrement of 0 (i.e. no change) was based on assumption. The model assumed that the proportion of patients of 64.76% (based on the complement of IVIG proportion).

Input description	Utility multiplier or decrement	Source
IVIG disutility	-0.01	The model assumed a proportion of patients (35.24%) was affected by this. In the model, the IVIG disutility of – 0.01 was calculated as = - 0.0006*(52/3), however this calculation was not explained. [1]
Weighted average for SCIG and IVIG	-0.004	Weighted value of the decrements and proportions reported above.
HSCT disutility within the first 100 days	-0.20	The submission reported a decrement of -0.20 based on Hornberger 2008 however the model used a decrement of -0.57 based on Sung 2003. [1] Using a utility decrement of -0.20 instead of -0.57 increased the ICER <1%.
Tonsillectomy disutility	-0.05	Tonsillectomy disutility was based on the disutility associated with complications (mainly haemorrhage) reported from Bagwell 2018. [1]

DLBCL = diffuse large B-cell lymphoma; HRQoL = health-related quality of life; IRT = immunoglobulin replacement therapy; IVIg = intravenous immunoglobulin; RCT = randomised controlled trial; SCIG = subcutaneous immunoglobulin
Utility decrements are represented by negative values. Utility multipliers are all other values.
[1] Source not provided/value could not be verified
Source: Table 3.32 of the submission and PHG LENIOLISIB CUA MODEL FINAL.xlsm

6.65 The Sub-committees considered that the approach to calculating acute and long-term decrements to utility was methodologically reasonable, however the use of various sources that could not all be verified or justified resulted in a high level of uncertainty in the values applied. There was substantial heterogeneity across all the sources informing utility values (e.g., different diseases, patient characteristics, treatments etc.) and none of these patient groups in these sources were APDS (acknowledging it is a rare disease). It was highly uncertain whether the manifestation utility decrements/multipliers used in the base case were accurately reflective of the disutility that would be experienced in APDS patients in practice and the Sub-Committees noted that some multipliers appeared implausible.

6.66 In addition, the model assumed that any severity reduction in manifestations associated with leniolisib treatment means the patient will not suffer any disutility from the manifestation. The Sub-Committees considered this was overly optimistic and the evidence to support this was not apparent.

6.67 The submission conducted two utility studies (the time trade off [TTO] and EQ-5D study) that gave utility values for health states representing a patient having manifestations however these values were not used in the model as the model structure adopted “treatment-based” health states rather than “manifestation-based” health states. For comparison, Table 18 compares the health state utility values from the EQ-5D study for various manifestation combinations with the baseline utility values in the leniolisib arm and SoC arm in the model given these manifestation combinations (at cycle 1/ age 15). Numerous differences were observed, such as the baseline utility for APDS was lower in the model compared to the EQ-5D study (0.76 to 0.88 vs 0.897, respectively) and the baseline utility of malignancies was substantially higher in the model compared to the EQ-5D study (0.6098 vs 0.278, respectively). Generally, the model values did not agree with the utility values in the EQ-5D study that was conducted by the submission and

therefore reflect a lack of external consistency. Additionally, in both the SoC arm in the model and the EQ-5D study, a patient who has most (or all) manifestations have a utility which is worse than death. It was unclear if this was reasonable.

Table 18: Comparison of baseline utility values in the EQ-5D study and the model given a patient experiences particular manifestations

	Mean baseline utility value		
Manifestation	**EQ-5D study**	**Model: leniolisib**	**Model: SoC**
Single manifestation health states (EQ-5D study only reported these ones as single)			
APDS only	0.897	0.7600	0.7600
APDS + infection	0.724	0.7521	0.7446
APDS + lymphoproliferation	0.755	0.6132	0.6132
APDS + bronchiectasis	0.679	0.6611	0.6123
APDS + malignancies	0.278	0.6098	0.6098
Combination health states			
APDS + infection + lymphoproliferation	0.642	0.605	0.598
APDS + infection + lymphoproliferation + bronchiectasis	0.461	0.506	0.450
APDS + infection + lymphoproliferation + cytopenia	0.609	0.516	0.508
APDS + infection + lymphoproliferation + GI manifestation	0.532	0.517	0.196
APDS + infection + lymphoproliferation + cytopenia + GI manifestation	0.347	0.428	0.107
APDS + infection + lymphoproliferation + bronchiectasis + cytopenia + GI manifestation + malignancies + fatigue + hearing loss	-0.109	0.159 (fatigue was not included in the model so not included in this estimate)	-0.209 (fatigue was not included in the model so not included in this estimate)
APDS + infection + lymphoproliferation + bronchiectasis + cytopenia + GI manifestation + malignancies + advanced lung disease + hearing loss	NA (advanced lung disease not in EQ-5D study)	0.159	-0.427

APDS = activated PI3Kδ syndrome; GI = gastrointestinal; NA = not applicable; SoC = standard of care
Notes: Baseline utility from the model calculated as the baseline utility at age 15 minus the respective disutilities from manifestations
Grey shaded cells indicate notable differences identified
Source: Table 5, p15 "Pharming Data on File - 2024 - Healthcare professional valuation of health states"; 'Leniolisib model engine' and 'SoC model engine' worksheet from the model PHG LENIOLISIB CUA MODEL FINAL.xlsm

6.68 The utility at age 16 (i.e., cycle 1) was 0.6683 in the leniolisib arm compared to 0.3885 in the SoC arm (which accounts for the proportion experiencing manifestations). The utility of SoC decreased over the time horizon compared to the leniolisib arm, for example, at age 31 the SoC utility was 0.09 compared to 0.6939 in leniolisib at the same age (utility increased in some cases for leniolisib). This suggested that patients in the SoC arm have almost half the utility compared to patients on leniolisib after 1 year of treatment, which was a strong assumption given no utility data from the trial was used. Even if it was assumed that the comparative benefit from the trials translated to QoL benefits, the comparative trial data was only 12 weeks and therefore did not even inform a complete cycle (one year).

6.69 Health care resource use (HCRU) and associated costs were included in the model for leniolisib treatment, additional treatment costs, manifestations associated with APDS and patient monitoring. Leniolisib treatment costs accounted for the vast majority of the total costs for the leniolisib arm; no other cost category accounted for more than [redacted]% of the total incremental cost (i.e. less than [redacted]/[redacted]th of the incremental impact of leniolisib costs, which accounted for [redacted]% of the total incremental cost). Due to this, the ICER was not sensitive to any other cost input except for changes in the price or utilisation of leniolisib.

6.70 The key drivers of the model are presented in Table 19.

Table 19: Key drivers of the model

Description	Method/Value	Impact [Base case: $[redacted] /QALY gained.]
Cost of leniolisib	Leniolisib drug costs are the main driver of the model and dwarf every other cost inclusion. In the model, the cost of leniolisib acquisition was $[redacted] - million. A full year of treatment of leniolisib would cost $[redacted]	Extremely high.
Time horizon	The lifetime time horizon used in the model was optimistic, especially considering that there was only 12 weeks of comparative data for leniolisib.	High, favours leniolisib. Use of a 10-year time horizon increased the ICER by [redacted]% and use of a 20-year time horizon increased the ICER by [redacted]%.
Rates of manifestations	Reduction in manifestation rates were based primarily on non-comparative single arm observational data. Some of the inputs could not be verified, and some strong assumptions were made in relation to the reductions in incidence and resolution of manifestations for patients receiving leniolisib, increasing uncertainty.	Moderate, favours leniolisib. Assuming no difference in lymphoproliferation (HR = 1 and 0% resolution) increased the ICER by [redacted]% and assuming no difference in GI manifestations increased the ICER by [redacted]%. Other manifestations each had an impact of around 5%.
Utility decrements	The model assumed that any severity reduction in manifestations associated with leniolisib treatment means the patient will not suffer any disutility from the manifestation (i.e. utility multiplier of 1 for the proportion who were assumed to be improved), which contributed to incremental utility differences between leniolisib and SoC in the manifestation tunnel states.	Moderate, favours leniolisib. Use of a GI utility multiplier of 0.75 increased the ICER by [redacted]% and use of a lymphoproliferation utility multiplier increased the ICER by [redacted]%.
Starting Age	The submission assumed a start age of 15 years based on ESID registry data. However, the proposed PBS restriction would allow patients to use leniolisib from age 12 years and patients in the Australian APDS case series had a median age of 25 years.	Moderate. Uncertain which direction it favours. Changing the start age to 12 years resulted in a [redacted]% increase in the ICER, and changing the starting age to 25 years decreased the ICER By [redacted]%.

HR = hazard ratio; GI = gastrointestinal; ICER = incremental cost effectiveness ratio; SoC = standard of care
Source: Constructed during the evaluation using *PHG LENIOLISIB CUA MODEL FINAL.xlsm*.
The redacted values correspond to the following ranges:
[1] *$855,000 to < $955,000*

6.71 The submission presented a stepped economic evaluation as presented in Table 20. The results of the stepped economic evaluation could not be verified during the evaluation. Only the final step could be replicated using the economic model provided. The base case ICER was $855,000 to < $955,000/QALY.

Table 20 :Stepped economic evaluation

Steps	Incremental costs ($)	Incremental health outcomes	ICER ($/QALYs)
1) Study 2201 Part II results and trial horizon	[redacted]	NA	NA
2) Study 2201E1+EAP trial results included. 6-year time horizon		NA	NA
3) Introduction of ESID registry		0 LYs	NA
4) Introduction of utilities and manifestations costs		0.15 QALYs	[redacted][1]
5) Introduction of HRs, resolution and reduction of severity of manifestations for leniolisib		1.27 QALYs	[redacted][1]
6) Introduction of relative risk of mortality versus the general population for leniolisib		1.73 QALYs	[redacted][1]
7) Imputation and extrapolation to a lifetime horizon		7.13 QALYs	[redacted]

ICER = incremental cost-effectiveness ratios; LYs = life years; NA = not applicable; QALYs = quality adjusted life years; SoC = standard of care

Source: Table 3.44, pp 266 of the submission

Note: with the exception of step 7 (the base case), the results of the other steps could not be verified during the evaluation

The redacted values correspond to the following ranges:

[1] *> $1,055,000*

[2] *$855,000 to < $955,000*

6.72 The results of key sensitivity analyses are summarised in Table 21.

Table 21: Scenario analysis

	Inc cost ($)	Inc QALYs	ICER ($/QALY)	Inc LYG	% change
Base case	[redacted]	**7.13**	[redacted][1]	**3.17**	**0**
Time horizon = 10 years (BC: lifetime)		2.78	[redacted][2]	0.42	[redacted]%
Time horizon = 20 years (BC: lifetime)		4.80	[redacted][3]	1.27	[redacted]%
Time horizon = 30 years (BC: lifetime)		6.00	[redacted][1]	2.02	[redacted]%
Start age = 12 years (same as restriction) (BC: 15 years)		6.86	[redacted][1]	3.03	[redacted]%
Start age = 25 years (as per Australian APDS case series report) (BC: 15 years)		7.94	[redacted][4]	3.33	-[redacted]4%
Assume 100% discontinuation in year 1 (BC: 2.55%)		2.11	[redacted][5]	0.02	-[redacted]3%
Assume discontinuation = 5% (BC: 2.55%)		5.83	[redacted][4]	2.36	-[redacted]%
Post-discontinuation manifestation risk "4. Catch up SOC" (BC: "2. Return to starting age risk")[a]		6.88	[redacted][1]	3.17	[redacted]%
Assume "4. Catch up SOC"[a] + 100% discontinuation for manifestation and additional treatments		0.37	[redacted][6]	0.02	-[redacted]%
GI utility multiplier = 0.75 (BC: 0.47)		6.15	[redacted][3]	3.17	[redacted]%
GI utility multiplier = 0.57 (BC: 0.47)		6.78	[redacted][1]	3.17	[redacted]1%
Lymphoproliferation utility multiplier = 0.91 (BC: 0.80)		6.30	[redacted][3]	3.17	[redacted]%
Excluding age-related utility decrements (BC: Include)		6.54	[redacted][1]	3.17	[redacted]%
Lymphoproliferation HR = 1 and 0% resolution (BC: HR = 0 and 96% resolution)		5.11	[redacted][2]	3.17	[redacted]%
GI manifestations HR = 1 and 0% resolution (BC: HR = 0 and 36% resolution)		6.55	[redacted][3]	3.17	[redacted]%
Malignancies HR = 1 (BC: HR = 0.41)		6.84	[redacted][1]	3.17	[redacted]%
Lymphoproliferation resolution rate = 0.48 (BC = 0.96)		6.26	[redacted][3]	3.17	[redacted]%
Survival, leniolisib RR versus general population = 0.9 (BC: 0.98690)		6.19	[redacted][1]	1.65	[redacted]%
Survival, leniolisib RR versus general population = 0.8 (BC: 0.98690)		5.11	[redacted][3]	-0.11	[redacted]%

BC = base case; GI = gastrointestinal; HR = hazard ratio; ICER = Incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality adjusted life year.

[a] The base case "2" corresponds to the assumption that post-discontinuation manifestation risk of will return to starting age risk (see paragraph 6.51), the sensitivity of changing this assumption to "4", corresponds to "Catch-up to SoC cumulative incidence based on the duration of tx" and the assumption changes such that only patients on who remain on leniolisib for 10+ years return to starting age risk following discontinuation.

Text in italics indicate values calculated during the evaluation

Source: Calculated during the evaluation using PHG LENIOLISIB CUA MODEL FINAL.xlsm

The redacted values correspond to the following ranges:

[1] *$855,000 to < $955,000*

[2] *> $1,055,000*

[3] *$955,000 to < $1,055,000*

[4] *$755,000 to < $855,000*

[5] *$55,000 to < $75,000*

[6] *$555,000 to < $655,000*

6.73 Noting this is a rare condition and the paucity of data available, the Sub-Committees considered a cost per responder approach may be informative in consideration of the cost-effectiveness of leniolisib to SoC. The Pre-PBAC response stated a cost per responder analysis was not feasible in this indication, as no universally accepted or validated response criteria exist in the literature, clinical guideline, or reimbursement criteria. Instead, the Pre-PBAC response proposed a reduction to the effective price of leniolisib ($, % discount compared with the submission proposed price) and a revised base case with alternative scenario analyses to address some of the Sub-Committee's concerns with modelling mortality.

Leniolisib cost/patient/year

Table 22: Drug cost per patient for leniolisib

	Proposed drug Trial dose and duration	Proposed drug Model	Proposed drug Financial estimates
Leniolisib, mean dose	70 mg, twice daily	70 mg, twice daily	70 mg, twice daily
Mean duration	12 weeks[a]	31.23 years	NR[b]
Cost/patient/month[c] (submission)	$	$	$[d]
Cost/patient/year[c] (submission)	$	$	$[d]
Cost/patient/year[e] (Pre-PBAC response)	$	$	$[d]

NR = not reported

[a] Study 2201 Part II provided 12 weeks of comparative data for leniolisib versus SoC.

[b] The financial estimates presented in the submission assumed patients received ongoing treatment with leniolisib but were subject to a discontinuation rate of 2.55% per year.

[c] Based on proposed leniolisib effective price = $ (mark-ups for private hospital setting were not included in calculations of the drug cost in the economic model or the financial estimates)

[d] Calculated using net total net cost of leniolisib to the PBS / number of patients treated in a year, using Year 2 data.

[e] Based on proposed leniolisib effective price = $ (without mark-ups for private hospital setting).

Source: Constructed during evaluation

Estimated PBS usage & financial implications

6.74 This submission was considered by DUSC at a joint meeting of ESC and DUSC. The submission used a 'top down' process to estimate the number of APDS patients diagnosed and treated in Australia based on Australian population estimates, published international APDS epidemiology estimates, commercial assumptions and information collected in the UK for the leniolisib NICE submission. However, it was unclear why this approach was adopted when the number of patients who have been diagnosed with APDS in Australia is known (18 patients diagnosed with APDS, and another 11 patients suspected of having APDS). The pre-PBAC response stated that it is estimated that there will be 12-15 patients on the early access program at the time of PBS listing.

6.75 Table 23 presents an overview of the data sources used for the financial estimates. The PBS costs, MBS costs and national blood authority (NBA) costs (associated with IRT) of SoC items in the financial estimates were consistent with the

economic evaluation, though the assumed proportions of utilisation could not be independently verified.

6.76 The Commentary noted that the submission assumed that leniolisib treatment access will grow the APDS treatment market due to greater clinician awareness and enhanced patient identification and diagnosis, with the 'diagnosed prevalence' of APDS assumed to grow in the initial years of leniolisib listing, before stabilising in 2030. However, the Commentary considered that the submission may have overestimated the number of patients with leniolisib in Australia, particularly in the later years of the financial estimates. In the PSCR the sponsor noted that under- and mis-diagnosis have been common issues in APDS, with more than 20% of patients diagnosed after a lymphoma and almost 70% diagnosed with other PIDs in historical cohorts. It is expected that greater patient and clinician awareness and identification via referral will occur with a listed indicated therapy. The sponsor also noted that increased diagnosis following new effective therapies is a common phenomenon with ultra-rare diseases/orphan drug treatments and that the ASCIA is developing strategies to improve the identification and diagnosis of Australians with IEIs, including APDS. The Sub-Committees considered that with increased awareness amongst clinicians and testing of patients it is possible that additional as well as less severe cases of the disease will be identified. The Sub-Committees considered that the increase in awareness and testing for APDS (given the awareness raising activities of both the sponsor and ASCIA) will in effect increase the prevalence rate in future years. The Sub-Committees noted that this appears to have already been captured in the financial estimates, which reflect increasing prevalence. The pre-PBAC response proposed revising the prevalence rates such that the prevalence reaches 1.9 patients per million by the 6th year of listing, remaining within estimates of prevalence in the literature (Vanselow 2023).

6.77 The Commentary noted that the proportion of patients discontinuing treatment could potentially be higher than expected as three out of the 18 patients in APDS Consortium data have discontinued for reasons other than efficacy. In the PSCR the sponsor noted that there had been, to date, no discontinuation due to loss of efficacy. The Sub-Committees considered that patients with less severe disease (particularly in comparison to those in the pivotal clinical trial) identified because of increased awareness of APDS and treatment availability may affect the discontinuation and persistence rates, particularly if adverse and side effects in these patients outweigh the clinical benefit. The Sub-Committees also noted that treatment of patients with a less severe disease phenotype would be expected to impact on the cost-effectiveness of leniolisib.

Table 23: Key inputs for financial estimates

Data	Value	Source	Commentary on the submission	Sub-Committees' comments
Eligible population				
Australian population	Yr 1: 24,162,218 Yr 2: 24,599,864 Yr 3: 25,028,274 Yr 4: 25,436,915 Yr 5: 25,827,361 Yr 6: 26,204,324	ABS high series Australian population projections 2025 to 2031	The number of patients receiving leniolisib was likely overestimated due to the use of ABS high series projections for the Australian population (rather than the medium series) and the use of APDS prevalence rates that increased over time. The total number of patients may be overestimated as there are currently 18 patients diagnosed with APDS in Australia, (11 patients suspected of having APDS).	The Sub-Committees considered that given the heterogeneity of APDS as awareness and diagnostic capabilities improve, genetic analysis driven by an increased clinical suspicion of APDS will lead to the possibility of identifying more people with APDS in Australia. A recent Italian study (Barzaghi et al) noted awareness among different specialists may improve referrals and timely recognition of the disease. The Sub-Committees noted that the prevalence in year 6 ([redacted] per million) is higher than the published literature estimates (Vanselow 2023). However, this may be reasonable accounting for increased awareness and diagnosis.
APDS prevalence rate	Yr 1: [redacted]/million Yr 2: [redacted]/million Yr 3: [redacted]/million Yr 4: [redacted]/million Yr 5: [redacted]/million Yr 6: [redacted]/million	Vanselow 2023 estimated the prevalence of APDS to be 1-2 per million. The submission assumed an equi-proportionate escalation between year 1 and year 6.		
Total patients	Yr 1: [redacted] Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	Calculated based on Australian population estimates for people aged 12 and above (ABS, 2023. Population Projections, Australia).		
Treatment utilisation				
Leniolisib uptake rate	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Commercial assumption based on expert clinician interviews in the UK.	Uptake rates were applied only to newly diagnosed patients (or patients newly receiving leniolisib in year 1) and patients who don't take up treatment in the year they are diagnosed are assumed to never consider leniolisib treatment in subsequent years.	The Sub-Committees considered that the uptake rates for Australia would be similar to UK values.
Leniolisib discontinuation rate	2.55%	Study 2201E (May 2024 data cut), and the leniolisib EAP (28 Nov 2024 data cut)	Magnitude consistent with the economic model but inappropriately only applied to new patients initiating leniolisib (incident patients in year 2-6 and prevalent patients in year 1) rather than an annual discontinuation rate, potentially leading to an overestimate in utilisation. Reinitiation was not considered in the financial estimates.	The Sub-Committees considered that reinitiation is likely.
Duration of treatment if	50% of annual volume	Assumption	Consistent with half cycle correction assumption in	The Sub-Committees noted this assumption.

Data	Value	Source	Commentary on the submission	Sub-Committees' comments
discontinued			financial model.	
Proportion of calendar year leniolisib is PBS listed	Yr 1: 50% Yr 2+: 100%	Assumption that leniolisib would be listed on the PBS in July 2026.	Unclear if appropriate. This would result in patients who discontinue in first year receiving only 25% (50% × 50%) of the number of packs for a year, which may be an underestimate.	The Sub-Committees considered that the estimate for year 1 was an underestimate.
Leniolisib persistence rate	100%	Persistence to therapy exhibited in Study 2201 Part II and Study 2201E1 and the international EAP.	Reasonable. Consistent with economic model.	The Sub-Committees noted that symptoms may return rapidly for people who are less adherent, and that high adherence is common in clinical trials. However, the Sub-Committees considered there is potential that the high adherence rate assumed may be an overestimation.
Reduction in PBS item treatments due to leniolisib treatment	50% for GI manifestations, bronchiectasis associated airway disease and advance lung disease	Assumption	It was unclear if this was reasonable, however was consistent with the economic model assumptions.	The Sub-Committees considered that these estimates are uncertain.
Costs				
Leniolisib	$[redacted]	Requested price	Consistent with requested listing price	The Sub-Committees noted these estimates.
Other PBS items	As per economic model	PBS prices	Reasonable.	
Co-payments	General $31.60 Concessional $7.70	Current co-payments	Reasonable.	
PBS general patient: concessional split	48.6%: 51.4%	PBS data for all S100 scripts in Australia 2023-24.	As no other drugs are used exclusively for APDS, this may be reasonable.	
PBS general: general safety net split	99.3%:0.7%			
Public: private hospital split	50:50	Assumption	It may have been more appropriate to use PBS data for a drug used for APDS such as sirolimus.	
NBA items				
SCIG/IVIG	$154.65	NBA price list, Intragam 10, 2.5g/25ml, CSL	NBA costs were consistent with the economic model, where it was also assumed that the cost of IVIG and SCIG were the same; however, they are not the same according to the NBA price	The Sub-Committees noted this estimate.

Data	Value	Source	Commentary on the submission	Sub-Committees' comments
			list.	

ABS = Australian Bureau of Statistics; EAP = Early Access Program; IVIG = intravenous immunoglobulin; NBA = National blood authority; NEP = National efficient price; PBS = Pharmaceutical Benefits Scheme; SCIG = subcutaneous immunoglobulin.
Source: Tables 4.1-4.5, 4.7-4.11 p283-299 of the submission.
The redacted values correspond to the following ranges:
[1] *<500*

6.78 Table 24 provides the estimated use and financial implications of leniolisib.

Table 24: Estimated use and financial implications

	2026	2027	2028	2029	2030	2031
Estimated extent of use						
APDS population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated 'new therapy' market share uptake rates vs SoC ([redacted]%)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent patients	[redacted][1]	-	-	-	-	-
Newly diagnosed patients	[redacted]					
Leniolisib uptake rate ([redacted]%-[redacted]%)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
New patients initiating leniolisib[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients receiving treatment, year beginning[b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients receiving SoC[c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients on treatment, year-end[d]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Packs[e]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]
Leniolisib net PBS cost (effective)	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]
Net difference in SoC costs with leniolisib listing	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net PBS cost (effective)	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]
Net MBS cost[g]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Hospitals and outpatient (AR-DRG, non-admitted items)	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
NBA	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net financial impact to healthcare system	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]
Revised estimates as per pre-PBAC response[h]	**2027 Year 1**	**2028 Year 2**	**2029 Year 3**	**2030 Year 4**	**2031 Year 5**	**2032 Year 6**
Year start pts	18.85	22.47	26.35	30.30	33.26	36.17
Discontinued	0.82	0.98	1.15	1.32	1.45	1.57
Year-end pts	18.03	21.50	25.21	28.98	31.81	34.60
Leniolisib net PBS cost (effective)	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]

AR-DRG = Australian Refined Diagnosis Related Groups; MBS = Medical Benefits Schedule; NBA = National Blood Authority; PBS = Pharmaceutical Benefits Scheme; SoC = standard of care.
Results are subject to rounding.

[a] Uptake rate multiplied by sum of newly diagnosed patients and prevalent patients. Note that the submission rounds up these values therefore from the third year onwards, effectively [redacted]% uptake assumed.
[b] Sum of Patients on treatment, year-end of the previous year plus newly diagnosed patients initiating leniolisib in current year.
[c] Patients receiving SoC = total APDS population - patients treated with leniolisib year beginning.
[d] Calculated as 97.45% (given 2.55% annual discontinuation rate) of patients receiving treatment, year beginning in current year.
[e] Figures incorporate assumption that patients receiving a full year of treatment receive 12.175 packs of leniolisib per year based on one pack providing 30 days of treatment (patients discontinuing treatment after 6 months receive 6.0875 packs per year) and a persistence rate of 100%.
[f] The submission assumed listing of leniolisib on the PBS Schedule would occur from 1 July 2026. Therefore, it was assumed that in the first year of listing, patients would receive 50% of the expected packs.
[g] Submission's MBS cost erroneously excluded MBS item 116 - Professional attendance at consulting rooms or hospital associated with prednisolone injections which have been recalculated during the evaluation.
[h] includes revised price, 4.35% discontinuation, revised prevalence, correction of minor calculation errors, [redacted]% ultimate market uptake, as per Pre-PBAC response – values not verified.
Source: Table 4.11, .4.32, 4.33, 4.39, 4.40, 4.44, 4.50, pp 299, 317-324, 332-333, 343 of the submission and UMP 1.0 Financial Table Workbook.
The redacted values correspond to the following ranges:
[1] *<500*
[2] *500 to < 5,000*
[3] *$0 to < $10 million*
[4] *$10 million to < $20 million*
[5] *$20 million to < $30 million*
[6] *net cost saving*

6.79 The total cost to the PBS of listing leniolisib was estimated to be 0 to < $10 million in Year 1 and $20 million to < $30 million in Year 6, and a total of $90 million to < $100 million in the first 6 years of listing. The submission also estimated minor cost savings due to reductions in PBS cost due to fewer estimated manifestations associated with leniolisib treatment.

6.80 The Commentary considered the financial estimates presented were uncertain as:

- The prevalence rate applied may be overestimated, as the prevalence was assumed to increase such that by year 5 of listing, the prevalence (2 per million) is double that of year 1 (1 per million), and the prevalence in year 6 (2.15 per million) is higher than the published literature estimates from which the prevalence was obtained (Vanselow 2023). See also Sub-Committee advice regarding prevalence in paragraph 6.76; and
- The annual discontinuation rate was only applied to newly initiated patients rather than applied every year, which may overestimate utilisation; but
- Uptake rates were also only applied to newly initiated patients i.e. patients diagnosed in year 1 are assumed to never initiate treatment in subsequent years if they do not start treatment in year 1, which may underestimate utilisation;
- It was assumed that leniolisib will be listed in July 2026, and as such only 50% utilisation was applied in year 1 of listing, which may not be reasonable and may underestimate the utilisation; and
- In the submission's calculations, patient numbers were rounded (in some cases rounded up) which, when considered in the context of small patient numbers and percentages, increased uncertainty in the estimates.

6.81 The pre-PBAC response presented revised financial estimates incorporating the revised proposed price ($), 4.35% discontinuation, prevalence per million for years 1 to 6, correction minor calculation errors, % ultimate market uptake (years commencing from 1 July 2026 listing).

6.82 The Sub-Committees did not consider that it was likely that the drug would be used beyond the requested restriction.

Quality Use of Medicines

6.83 The sponsor has conducted/planned several pre-listing and post-listing activities to support Quality Use of Medicines (QUM). This includes activities such as local advisory board meetings and engagement/collaboration with the Clinical Immunogenomics Research Consortium of Australasia (CIRCA) and the ASCIA. The submission stated that the sponsor aims to work closely with either the LSDP or Section 100 HSD unit in collaboratively communicating QUM via promotion and education of the requested restriction.

Financial Management – Risk Sharing Arrangements

6.84 The submission proposed an RSA, whereby when pack utilisation exceeds the proposed financial cap by %, % and %, respectively in forecast years, it will result in an equivalent reduction in the effective pack prices. The Sub-Committees noted there was a lack of clarity in the sponsor's proposed caps and application of rebates. The PBAC considered there was minimal risk of use outside the proposed patient population and a risk sharing arrangement was not required.

6.85 The submission noted that the open label extension Study 2201E1 (CCDZ173X2201E1) remains ongoing and is expected to provide longer term efficacy and safety data post listing, which can be provided, along with observational data in the Australian APDS population.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of leniolisib for the treatment of symptomatic APDS in adults and adolescents aged 12 years and older. In making this recommendation, the PBAC recognised the high unmet clinical need for treatment options for patients with APDS noting the condition results in substantial impacts on quality of life for patients and reduced life-expectancy. The PBAC was satisfied that leniolisib improves a range of immunity markers that are representative of the underlying disease activity for APDS and is therefore likely to result in clinically meaningful improvements in patient-relevant outcomes such as infections, lung disease,

lymphadenopathy and risk of lymphoma. The PBAC considered that the incremental cost-effectiveness was uncertain due to the limited data informing the economic model, but that in the context of this rare and life-limiting disease, leniolisib would be considered acceptably cost-effective with a price reduction that would result in an acceptable cost per patient per year. The PBAC noted this recommendation is in line with other treatments for rare diseases funded on the PBS and takes into account clinical need, available evidence, nature of the benefits, and size of the patient population.

7.2 The PBAC is satisfied that leniolisib provides, for some patients, a significant improvement in efficacy over the main nominated comparator, SoC, in the treatment of APDS.

7.3 The PBAC noted the high unmet clinical need for treatment options for patients with APDS given the substantial impacts on quality of life for patients and reduced life-expectancy. The PBAC noted the sponsor hearing and the consumer comments highlighting the high burden of disease and desire to access targeted, disease-modifying therapies for this condition.

7.4 The PBAC considered an Authority Required (written) restriction type would be appropriate for the initial treatment phase and an authority required (telephone/immediate assessment) restriction type for the continuing treatment phase, given the high cost of leniolisib. For this reason, the PBAC also considered it appropriate that prescribing is limited to immunologists or medical practitioners in consultation with an immunologist, with expertise in managing patients with primary immunodeficiencies or APDS.

7.5 The PBAC considered it would be appropriate for the initial restrictions to limit treatment to symptomatic patients in order to exclude those people who are asymptomatic carriers and may not benefit from treatment. The PBAC noted the difficulty outlining specific criteria for clinical assessments, which could potentially impact equitable and timely access to leniolisib. The PBAC considered it would be reasonable for the restrictions to not specify the assessments required for diagnosis and/or symptoms given the population is well understood and diagnosis is based on genetic confirmation.

7.6 The PBAC noted the proposed continuing restriction limited treatment to patients responding to treatment (defined by limiting progression of symptoms and/or resolution of symptoms) but no specific response criteria were proposed. The PBAC considered it reasonable to include a general response criterion for ongoing treatment requiring that patients are stable or responding to treatment, which would be based on clinical judgment and include consideration of immunological markers. The PBAC considered that it would also be reasonable for the restrictions to allow patients who had previously shown a response to leniolisib to reinitiate treatment under the continuing restrictions, negating the need for a separate

reinitiation listing. The PBAC noted that as there are no clearly defined stopping criteria it would be expected that patients who tolerate treatment would continue on life-long therapy, which is likely to be clinically appropriate given it is a disease-modifying treatment.

7.7 The PBAC noted the pre-PBAC response indicated 12-15 patients are expected to be receiving leniolisib through the EAP and considered it would be reasonable for patients receiving leniolisib under the EAP, or patients who had previously received treatment under the EAP, to initiate leniolisib under the initial treatment criteria. The PBAC also noted the switch from the EAP to PBS-funded leniolisib would not require demonstration of any response to or benefit with leniolisib, but ongoing treatment would require stable or responding disease.

7.8 The PBAC considered the clinical place for leniolisib is as a first line treatment option, in addition to existing SoC therapies for APDS (other than rituximab and mTOR inhibitors, which were excluded as concomitant treatments in Study 2201). The PBAC noted that leniolisib is the first disease-modifying therapy available for the treatment of APDS.

7.9 The PBAC accepted the submission's nominated main comparator, SoC. The PBAC noted that in clinical practice, leniolisib would be used in addition to, rather than replacing SoC, although the utilisation of different components of SoC may differ depending on whether a patient also receives leniolisib. The PBAC considered that sirolimus was not a primary comparator as it is effective in treating only some manifestations of APDS and is not used commonly in clinical practice in Australia.

7.10 The PBAC noted the the submission was primarily based on one phase 3 head-to-head RCT that compared leniolisib to placebo (as a proxy for SoC) in patients with APDS aged 12 to 75 years (Study 2201 Part II). The PBAC noted that the submission also relied on many post-hoc analyses where published data were lacking and considered these analyses were associated with a high risk of bias. The PBAC noted both the analyses of co-primary endpoints were underpowered not because of the number of patients recruited but due to the inclusion of fewer patients than anticipated in the analysis as a result of exclusion based on baseline measurements.

7.11 Study 2201 Part II demonstrated that leniolisib improves a range of immunity markers, including the co-primary endpoints (change in naïve B cells as a percentage of total B cells and change in both spleen volume and size) compared to placebo over 12 weeks. The PBAC considered the demonstrated improvements in surrogate outcomes, such as immune cell changes, provide a representation of the underlying disease activity for APDS, and are therefore likely to result in improvements in patient-relevant outcomes such as infections, lung disease (bronchiectasis), lymphadenopathy and risk of lymphoma. The PBAC noted the limitations of the evidence including the potential bias in some of the analyses

presented and the short duration of the comparative study but acknowledged the difficulty of obtaining high quality clinical evidence in APDS. The PBAC considered the availability of comparative data provided confidence in the clinical claim of superior comparative effectiveness of leniolisib over SoC.

7.12 The PBAC considered that the claim of non-inferior comparative safety over SoC was uncertain as there are limited comparative data available. The PBAC noted the TGA Delegate considered it likely that long term treatment with leniolisib will lead to the emergence of rarer adverse events associated with PI3Kδ inhibition in some patients. However, based on available evidence as presented in the submission, the incremental adverse events for patients receiving leniolisib appear to be manageable.

7.13 The submission presented a cost-utility analysis for the economic evaluation, based on the results of Study 2201 Part II with additional clinical data from Study 2201E, the leniolisib EAP and the ESID-APDS registry. The PBAC noted the submission's base case ICER for leniolisib + SoC versus SoC was $855,000 to < $955,000/QALY gained. The pre-PBAC response proposed an % reduction in the effective price for leniolisib which reduced the ICER to $755,000 to < $855,000$/QALY gained. The PBAC noted that there was a very high level of uncertainty associated with the ICER due to assumptions regarding the frequency and resolution of manifestations, the impacts of manifestations on QoL, and treatment discontinuation and ongoing treatment effect. Further the PBAC noted the Sub-Committees' advice that the model structure was not reliable for decision-making, and the base case ICER was likely heavily biased towards leniolisib. However, given the paucity of data available for this rare condition, the PBAC acknowledged that revising the model structure or inputs is unlikely to resolve the uncertainty associated with the modelled outcomes. The PBAC considered that the value proposition was difficult to assess with a traditional ICER due to the limited long-term clinical data and lack of long-term patient-relevant outcomes to inform the model, the small number of patients included in the trial, and the highly individualised manifestations of APDS.

7.14 The PBAC reflected on previous determinations made for other rare diseases where no effective alternative therapies were available. The PBAC compared the available evidence, nature of the benefits, ICERs, numbers of patients expected to be treated, and the cost per patient per year for leniolisib at the proposed price, with other high-cost treatments for rare diseases funded on the PBS. The PBAC considered that in the context of this rare and life-limiting disease, leniolisib would be considered acceptably cost-effective at a cost of not more than $ per patient per year. In providing this advice, the PBAC acknowledged that patients with less severe disease manifestation than those included in the economic model may be identified as a result of increasing awareness and diagnosis of APDS, as assumed in the financial estimates (see paragraph 7.15).

7.15 The PBAC noted the submission used an epidemiological approach to estimate the financial impact of listing leniolisib. The PBAC considered the financial estimates relatively certain given the diagnosis of APDS is well-defined, the number of patients is known due to the registry, and it is highly likely patients will remain on treatment. The PBAC noted the estimated number of patients in year 1 of the listing was higher than the number of known Australian APDS patients but was consistent with estimates that included patients suspected of having APDS. The PBAC considered that with greater awareness and testing of the disease and the likely identification of less severe cases, usage could increase over the forward years, as was captured in the submission's prevalence assumptions. The PBAC considered that the submission's estimated patient numbers were reasonable. The PBAC noted that the financial estimates require corrections (as per paragraph 6.80) to the application of the annual discontinuation rate and uptake rates, and year 1 utilisation should be increased from 50% to 100%. In addition, the format of the calculations should be revised to conform to standard requirements.

7.16 The PBAC considered that, with the amendments to the restriction criteria outlined in Section 3, there was minimal risk of use outside the proposed patient population and a risk sharing arrangement was not required where the cost of leniolisib is reduced to an acceptably cost-effective level. However, the PBAC advised that the utilisation of leniolisib should be reviewed once listed on the PBS to ensure patient numbers reflect the estimates in the submission, given that the estimates assumed increasing prevalence, and there is potential for identification and treatment of patients with less severe disease. The PBAC considered more defined restriction criteria for initiation and continuation of treatment may be required if utilisation leniolisib is substantially above the estimates.

7.17 The PBAC recommended that leniolisib should not be treated as interchangeable on an individual patient basis with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.

7.18 The PBAC advised that leniolisib is not suitable for prescribing by nurse practitioners. The PBAC advised that leniolisib is suitable for prescribing by medical practitioners only.

7.19 The PBAC advised the Early Supply Rule should not apply to leniolisib.

7.20 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for leniolisib:

a) The treatment is expected to result in substantial and clinically meaningful improvements over SoC in patient-relevant outcomes such as infections, lung disease, lymphadenopathy and risk of lymphoma;

b) The treatment is expected to address a high and urgent unmet clinical need as there

are currently no disease-modifying therapies available;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.21 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive PBAC recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item.

<table>
<tr><th colspan="2">MEDICINAL PRODUCT
medicinal product pack</th><th>PBS item code</th><th>Max. qty packs</th><th>Max. qty units</th><th>№. of Rpts</th><th>Available brands</th></tr>
<tr><td colspan="7">LENIOLISIB</td></tr>
<tr><td colspan="2">leniolisib 70 mg tablet, 60</td><td>NEW/ Public
MP</td><td>1</td><td>60</td><td>5</td><td>Joenja</td></tr>
<tr><td colspan="2">leniolisib 70 mg tablet, 60</td><td>NEW/ Private
MP</td><td>1</td><td>60</td><td>5</td><td>Joenja</td></tr>
<tr><td colspan="7"></td></tr>
<tr><td colspan="7">Restriction Summary [new1] / Treatment of Concept: [new1]:</td></tr>
<tr><td colspan="2" rowspan="4">Concept ID (for internal Dept. use)</td><td colspan="5">Category / Program:
☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)</td></tr>
<tr><td colspan="5">Prescriber type:
☒Medical Practitioners</td></tr>
<tr><td colspan="5">Restriction type:
☒Authority Required (FULL assessment) in writing only via OPA/post/HPOS upload)</td></tr>
<tr><td colspan="5">Authority type: ☒ Complex Authority Required (CAR)</td></tr>
<tr><td rowspan="2">Prescribi</td><td></td><td colspan="5">Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</td></tr>
<tr><td></td><td colspan="5">Administrative Advice: No increase in the maximum number of repeats may be authorised.</td></tr>
</table>

		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 70(270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation a applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authoritie system (see www.servicesaustralia.gov.au/hpos) Alternatively applications for authority to prescribe can be submitted online using the form upload facility i Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Episodicity: [blank]
		Severity: [blank]
		Condition: Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)
		Indication: Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)
		Treatment Phase: Initial treatment
		Clinical criteria:
		Patient must not have previously received PBS-subsidised treatment with this drug for this condition.
		AND
		Clinical criteria:
		Patient must have a diagnosis of APDS, confirmed by genomic or genetic testing demonstrating a pathogenic or likely pathogenic gain-of-function variant in the PIK3CD gene or a pathogenic or likely pathogenic loss-of-function variant in the PIK3R1 gene
		AND
		Clinical criteria:
		Patient must have symptomatic APDS prior to initiating treatment with this drug
		Treatment criteria:
		Patient must be treated by a clinical immunologist or in consultation with a clinical immunologist with expertise in managing patients with primary immunodeficiencies or APDS specifically.
		Treatment criteria:
		Patient must not be undergoing concomitant treatment with any of the following: (i) rituximab (ii) mTOR inhibitors
		Population criteria:
		Patients must be aged 12 years or over
		Prescribing instructions: If the application is submitted through HPOS form upload or mail, it must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
		Prescribing instructions: In the relevant PBS Authority Application form, specify the following: (i) Report confirming evidence of APDS with genetic diagnosis (as outlined under Clinical criteria) for gain of function mutations around PIK3CD and PIK3R1 Confirm that genetic testing has been completed to demonstrate the following in support of an APDS diagnosis:

	(i) demonstrating a pathogenic or likely pathogenic gain-of-function variant in the PIK3CD gene; or (ii) demonstrating a pathogenic or likely pathogenic loss-of-function variant in the PIK3R1 gene Quote the date, pathology provider name and any unique identifying serial number/code that links the genetic test result to the patient.
	Prescribing instructions: An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 5 months of therapy and no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment after 6 months of the initial treatment course.
	Prescribing instructions: The assessment of response to treatment must be documented in the patient's medical records.
	Administrative Advice: An outcome on the authority application is not immediate but will follow in due course. Electronic upload is encouraged to reduce processing time.

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
LENIOLISIB						
leniolisib 70 mg tablet, 60		NEW Public MP	1	60	5	Joenja
leniolisib 70 mg tablet, 60		NEW Private MP	1	60	5	Joenja
Restriction Summary [new2] / Treatment of Concept: [new2]:						
This column – for Dept. use		**Category / Program:**)☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
		Prescriber type: ☒Medical Practitioners				
		Restriction type: ☒Authority Required (immediate assessment)				
		Authority type: ☒ Complex Authority Required (CAR)				
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
		Administrative Advice: No increase in the maximum number of repeats may be authorised.				
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).				
		Episodicity: [blank]				
		Severity: [blank]				
		Condition: Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)				
New I1		**Indication:** Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)				
		Treatment Phase: Continuing treatment or reinitiation after a break in therapy				
		Clinical criteria:				
		Patient must have previously received PBS-subsidised treatment with this drug for this condition				
		AND				
		Clinical criteria:				
		Patient must have stable or responding disease *to* PBS-subsidised treatment with this drug for this condition under the initial treatment restriction if the patient has not had a treatment break*;*				
		OR				
		Patient must have stable or responding disease to the most recent PBS-subsidised treatment with this drug for this condition prior to a treatment break				
		Treatment criteria:				
		Must be treated by a clinical immunologist or in consultation with an immunologist with expertise in managing patients with primary immunodeficiencies, or APDS specifically.				
		Treatment criteria:				

New TC2.1	Patient must not be undergoing concomitant treatment with any of the following: (i) rituximab; (ii) mTOR inhibitors
	Prescribing instructions: An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 5 months of therapy and no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment after 6 months of the initial treatment course.
	Prescribing instructions: The assessment of response to treatment must be documented in the patient's medical records.
	Prescribing instructions: If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be documented in the patient's medical records.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Pharming Australia Pty Ltd and the Australian APDS community acknowledge the comprehensive evaluation of this submission by the PBAC and its sub committees, and the constructive recommendations of the committee to enable APDS patients and their clinicians potential access to the first TGA approved and PBAC recognised, targeted and disease modifying medicine Joenja® (leniolisib) for this devastating disease via the PBS, Section 100 – HSDP. The sponsor has formally notified the Department of Health, Disability and Ageing of our intent to work with all Australian Government to ensure a prompt listing based on these PBAC recommendations.