NICE National Institute for Health and Care Excellence

NICE guidance

Leniolisib for treating activated phosphoinositide 3-kinase delta syndrome in people 12 years and over

Highly specialised technologies guidance

Published: 23 April 2025

www.nice.org.uk/guidance/hst33

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendation

1.1 Leniolisib is recommended, within its marketing authorisation, for treating activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over. Leniolisib is recommended only if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

APDS is an ultra-rare genetic condition that can severely affect the quality of life of people with the condition, and their families and carers, and can significantly shorten life. It can cause organs and lymph nodes to swell and the body's immune system to attack healthy tissue. People with the condition are also at high risk of serious infections, and it can increase the risk of cancer. There are no licensed treatments for APDS. Standard care includes antimicrobial treatment, surgery, immunosuppressants, immunoglobulin (antibody) replacement therapy, and stem cell transplants.

Clinical trial evidence shows that leniolisib, compared with placebo plus selected standard care treatments, reduces the size of people's lymph nodes and increases levels of immune cells called B cells.

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, leniolisib is recommended.

2 Information about leniolisib

Marketing authorisation indication

2.1 Leniolisib (Joenja, Pharming) is indicated for 'the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and paediatric patients 12 years of age and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for leniolisib.

Price

2.3 The list price of leniolisib is £36,670 per pack of 60 tablets (excluding VAT; NHS Business Services Authority [NHSBSA] dictionary of medicines and devices [dm+d] browser; accessed October 2025).

2.4 The company has a commercial arrangement. This makes leniolisib available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Pharming, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) is a rare condition that was first recognised as a unique disease in 2013. APDS affects the body's immune system, which means that people with APDS have a reduced ability to fight infections. It is caused by gene mutations that cause the protein PI3K delta to become overactive. PI3K delta is found in cells and affects how cells develop and mature. When overactive, cells such as white blood cells are either over or underproduced and do not develop properly. As a result, the immune system cannot work correctly. APDS is characterised by immune dysregulation and immune deficiency, which are associated with various manifestations. In early childhood, manifestations can include repeated lung infections and problems growing and developing. Manifestations are age dependent and, as people age, the disease progresses and people have more manifestations, which can become more severe. Immunodeficiency UK reported that manifestations with an extreme impact included bronchiectasis (50.0%), respiratory infections (45.5%) and chronic cough (45.5%). Clinical experts supported this, reporting that by adulthood, it is common for people with APDS to have lung disease. These manifestations can lead to irreversible organ damage and an increased risk of developing lymphoma. APDS manifestations often lead to premature death, with a median survival of 44 years according to the latest European Society for Immunodeficiencies (ESID) registry data. The committee concluded that APDS is a rare lifelong condition that can affect length of life.

Heterogeneity of APDS

3.2 APDS is a progressive disease that presents differently in every individual. There is large variation in the diagnosis age, symptoms and severity of APDS. For example, the median age at the first manifestation is 1 year, but the median age of diagnosis is around 9 years according to the UK Primary Immunodeficiency Registry. Some people may have multiple manifestations that severely affect their quality of life and can significantly reduce their life expectancy. For others, APDS can be a condition associated with few symptoms, and be diagnosed only after a family member is diagnosed. This was supported by a patient expert, who explained that her child had APDS, but that she had only recently been diagnosed herself. This illustrates that, even within families, APDS diagnosis and symptom burden can be very heterogeneous. The clinical experts highlighted that a late diagnosis does not always mean that a person's life has not been impaired by APDS. They added that many people will have been misdiagnosed or have not yet had a diagnosis for their symptoms. They explained that this is because of the variability in APDS's presentation, its similarity to other immunodeficiency disorders and its relatively recent recognition as a unique condition. The clinical experts also noted that they expect the true incidence of APDS to be higher than currently reported. The committee concluded that APDS is a very heterogeneous condition, that affects people to different extents.

Effects on quality of life

3.3 The accumulation of multiple manifestations over time can impact the quality of life of people with APDS and their carers, family and friends. The patient experts explained that APDS has a significant impact on their daily life, mental health and quality of life. They noted that APDS has broad and substantial emotional effects including stress, depression, fatigue and constant anxiety about progression, often accompanied by a sense of hopelessness about their future. Immunodeficiency UK and NICE ran a survey to help understand the impact of APDS on people with the condition and carers. Only 31% of people reported that they had satisfaction with their quality of life. They explained that to avoid infections, people often have to make lifestyle adjustments such as social distancing. As a result, they are often unable to socialise, go to work or school, and have difficulties forming and maintaining relationships. People with APDS

described themselves as feeling drained both physically and mentally from having various manifestations and needing frequent hospitalisations. The survey reported that APDS has a significant impact on individuals and families in terms of time spent in hospital and managing appointments. Many people with APDS also need physical and emotional support from carers because of the severe and complex manifestations (see section 3.1). The patient experts stated that their caring responsibilities negatively affect their emotional wellbeing, relationships with loved ones and their daily lives, for example, by forcing them to reduce their working hours. They highlighted that APDS can be inherited, so some families have more than 1 family member with APDS. They said that this compounds the complexity of managing the condition, for example, with an unwell parent having to look after an unwell child. In response to consultation, Immunodeficiency UK provided additional evidence supporting the significant impact APDS has on carers and highlighted the positive effect that leniolisib could have on the whole family. The committee concluded that APDS is likely to reduce the quality of life for people with the condition and their families and carers.

Clinical management

Treatment options

3.4 There are currently no licensed medicines for APDS. UK clinical management is mostly limited to supportive care, which aims to treat the symptoms and manifestations of APDS rather than the cause. This includes antimicrobials, immunosuppressants, immunoglobulin (antibody) replacement therapy, surgeries and other procedures. Off-label mammalian target of rapamycin (mTOR) inhibitors are also used to treat APDS. The Immunodeficiency UK survey highlighted that people can have multiple treatments, with some reporting up to 6 ongoing medications. A potential curative treatment for eligible people is a haematopoietic stem cell transplant. The clinical experts explained that in practice, they are hesitant to offer this because of the risks associated with transplants. This is particularly the case for adults, in whom more damage has likely accumulated and so there may be more risks than benefits. So haematopoietic stem cell transplants are mainly reserved for children with APDS and very few people aged 12 years and over have them.

A submission from NHS England highlighted that the treatment pathway is well defined, despite there being no UK APDS clinical guidelines. It explained that the treatment approach depends on the clinical features of the person and that their condition is usually treated collaboratively between centres with shared expertise. For this reason, there is not expected to be significant variation between treatment approaches across the NHS. This was supported by the clinical experts who explained that, when possible, they take a holistic approach to treatment, so it is important for people with APDS to establish a link with a specialist centre as early as possible. They also emphasised the clinical heterogeneity of APDS (see section 3.2), describing how they have to offer personalised treatments, even within families, because APDS can present so differently. Despite the treatments available, not all manifestations are alleviated, and people can still be at high risk of developing lymphoma and dying in early life. Immunodeficiency UK reported that people with APDS face demanding treatment plans, including lengthy and regular hospital stays for invasive procedures. This adds extra stress and upset to the daily lives of people with APDS and their families (see section 3.3). The committee noted that the treatment of APDS is determined on a case-by-case basis, and that current clinical management can be demanding and may only relieve symptoms. It concluded that there are several treatments used to manage symptoms of APDS, but there is an unmet need for an effective treatment that addresses the cause of APDS.

Treatment positioning of leniolisib

3.5 The company positioned leniolisib as a treatment for APDS in people 12 years and over, in line with its marketing authorisation (see section 2.1). The summary of product characteristics for leniolisib states that the recommended dosage of 70 mg twice daily is for people aged 12 years and over weighing 45 kg or more. There is no recommended dosage for people who weigh less than 45 kg. The leniolisib clinical trials also only included people who weighed 45 kg or more (see section 3.6). The EAG highlighted that the British National Formulary mean weight for a 12-year-old is 39 kg. It explained that the dosing of leniolisib means that people who may otherwise be eligible may be excluded from having it. The committee questioned how healthcare professionals would deal with this if leniolisib was recommended. The company explained that there are 2 ongoing

trials for children aged between 1 and 11. In future it hopes to extend the marketing authorisation to younger people using weight-based dosing. The company highlighted that the 45-kg restriction was not based on safety issues but on expert advice from the global leniolisib trial. It noted that if leniolisib was recommended before the licence was extended, in the interim period it may be available for off-label use on a compassionate basis. This means that the people who may be excluded from having leniolisib, those aged 12 years and over but weighing less than 45 kg, may still be able to access it. The committee noted that people who weigh less than 45 kg may have access to leniolisib off-label. But it concluded that because this weight was outside of the current dosing recommendations, it would not be included in the recommendation.

Clinical effectiveness

Clinical trial evidence

3.6 The company's main clinical evidence came from Study 2201 part 2, a phase 3, triple-blind, 12-week randomised controlled trial (n=31). It investigated the efficacy of leniolisib (70 mg twice daily, n=21) compared with placebo plus selected symptomatic treatments (n=10). The trial included people aged 12 to 75 years with a documented APDS genetic PI3K delta mutation, who weighed 45 kg or more. It was done across multiple sites globally, including the UK. The primary outcome measures were a change from baseline in the proportion of naive B cells as a percentage of the total B cells, and the change from baseline in the index lymph node size. These were surrogate primary endpoints to measure the impact of leniolisib on normalising the immune system and reducing lymphadenopathy (enlarged lymph nodes). Key secondary outcomes included spleen size reduction, non-index and index lesions, patient-reported outcomes and adverse events.

The company provided further clinical trial evidence from:

- Study 2201 part 1 (n=6), a 12-week, single-arm, within-participant, dose-escalation trial that informed the fixed dose of leniolisib, and
- Study 2201E1 (n=37), an ongoing long-term extension trial, in which data was

collected for up to 6 years and 3 months.

After 12 weeks in Study 2201 part 2, leniolisib significantly increased the proportion of naive B cells as a percentage of total B cells (difference in adjusted means: 37.30, standard error: 5.74, [95% confidence interval: 24.06 to 50.54], p=0.0002). The improvement in proportion of naive B cells continued in Study 2201E1, with an increase in the percentage of naive B cells at each time point. This indicated that leniolisib can sustain normalisation of the immune system. After 12 weeks, leniolisib also resulted in a statistically significant decrease in lymphadenopathy (difference in adjusted means: -0.25, standard error: 0.06, [95% confidence interval: -0.38 to -0.12], p=0.0006). In Study 2201E1 the effects of leniolisib on index lesion size were also sustained.

Additional data sources

3.7 The company provided additional clinical evidence and analyses from several other data sources to support the main clinical trial evidence (see section 3.6) and to inform the economic model. This included data from:

- ESID registry – an international registry of people of all ages with primary immunodeficiencies, including a cohort with a genetic confirmation of APDS. The company did various analyses of ESID data to investigate the characteristics of APDS.
- Expert consultancy project – the company ran 4 exercises, each with 5 clinical experts with APDS experience from the UK, Europe and Canada to address various areas of uncertainty in the evidence base and to validate key assumptions. This included an expert elicitation exercise, an EQ-5D-5L vignette study, and a qualitative and quantitative survey.
- Early Access Programme (EAP) survey – the global EAP for leniolisib provides leniolisib to people with APDS who were unable to enter the clinical trial. Twenty-one physicians completed questionnaires on behalf of 30 out of the 40 people having leniolisib through the EAP. The survey was done to capture additional data on the clinical benefits of leniolisib across clinically relevant domains, including cytopenia, lymphoproliferation, infections, chronic fatigue,

and gastrointestinal and pulmonary manifestations.

- Indirect treatment comparison (ITC) – the company did an ITC to validate the conclusions about leniolisib from Study 2201 part 2 (see section 3.6), using a standard care arm that better represented current UK clinical management. This was because the comparator arm in the trial restricted the use of certain treatments for APDS, such as immunosuppressive medication. Leniolisib data from Study 2201E1 was compared with data from eligible people with APDS from the ESID registry. Key endpoints were the reduction in respiratory infections and serum immunoglobulin levels. To minimise the baseline differences between treatment groups, inverse probability of treatment weighting was used to control for covariates identified by clinical experts as potential treatment effect modifiers. This included age, sex, baseline use of immunoglobulin replacement therapy and baseline serum immunoglobulin levels. The results showed that, compared with standard care, leniolisib reduced serum immunoglobulin levels and statistically significantly lowered rates of respiratory infections. The EAG agreed that the results showed improvements consistent with Study 2201 part 2. But it noted that the eligibility criteria for the control group did not match the trial population and that the treatment groups were not always balanced for at baseline.

Uncertainties in the key clinical trial evidence

3.8 In Study 2201 part 2, nearly all of the participants had concomitant treatments alongside leniolisib or placebo. This included steroids, antimicrobials, immunoglobulin replacement therapy and antibiotics. But some treatments considered to be standard care were not permitted, including some immunosuppressive medications such as rituximab, and mTOR inhibitors. The company said that this was because these treatments increase the risk of infection, and prohibiting them would allow an unbiased assessment of efficacy in the treatment of lymphadenopathy, a key endpoint in the trial (see section 3.6). The EAG had concerns about the generalisability of the comparator arm because it excluded treatments considered established clinical management of APDS in the UK (see section 3.4). This meant that the treatment regimen in the placebo group was less intensive than clinical practice, which was a substantial limitation when trying to estimate the relative effectiveness of leniolisib. The company

acknowledged this but reported that its clinical experts had agreed that they would not prescribe some immunosuppressive medications alongside a PI3K delta inhibitor like leniolisib. So the concomitant medication used in the trial generally reflected how leniolisib would be used in practice. The clinical experts explained that they would use either leniolisib or an immunosuppressant. They noted that they would only consider using them together in an extreme situation.

The EAG acknowledged that the company's ITC partially addressed the concerns it had about the generalisability of the trial (see section 3.7). It also noted that Study 2201 part 2 had other uncertainties. These included baseline imbalances with previous treatment use and baseline manifestation rates, the novelty of the surrogate primary endpoints and the small sample size. It agreed with the company that balancing baseline differences in heterogenous and ultra-rare populations is difficult. But it highlighted that the data showed that people in the control arm were more severely impacted at baseline than people in the leniolisib arm. Together, these factors introduced uncertainties about the true magnitude of effect, and if used in the model could have overestimated the cost effectiveness of leniolisib. The company understood these concerns, highlighting the difficulty of collecting high-quality data from a very small population. It reassured the committee that its clinical experts thought that the baseline characteristics were generalisable to people seen in routine practice and in the ESID registry. The committee recognised the challenges of collecting data in rare conditions and considered the clinical experts' testimonies of how leniolisib would be used in UK clinical practice. It concluded that Study 2201 part 2 was acceptable for decision making but noted that there were still unresolvable uncertainties in the evidence that should be considered in decision making.

Economic model

Company's modelling approach

3.9 The company submitted a cohort state transition model with 3 mutually exclusive treatment states: alive on leniolisib treatment, alive not on leniolisib (on current clinical management, also referred to as standard care), and death. People in the leniolisib arm entered the model on treatment and stayed there unless they

stopped leniolisib treatment. People in an alive treatment state (either on or not on leniolisib treatment) could transition to the death state at any time based on overall cycle-specific probabilities of death. In the alive treatment states, the prevalence of manifestations and treatment use was estimated using a partitioned approach. This was to capture the progressive nature of APDS, which is characterised by the age-dependent onset of multiple complex manifestations across multiple organ systems (see section 3.1). Costs and utilities were calculated in each 1-year cycle based on modelled manifestations and treatment use and were accrued over a lifetime time horizon. The benefits of leniolisib were modelled by the resolution or reduced incidence and severity of manifestations and treatment use. The committee noted that using a treatment-state model rather than a health-state model had created some complexities in the modelling of the leniolisib treatment effect (see section 3.10 and section 3.13). It also noted that the structure of the model did not allow the EAG to explore changes to assumptions, which is necessary to inform committee decision making (see section 3.13). In the first meeting, the committee concluded that it would have preferred to see a health-state model that could be fully explored.

In response to consultation, the company provided a revised model with an altered structure to enable post-discontinuation events (see section 3.14) to be explored. This replaced the single leniolisib discontinuation health state (alive not on leniolisib) with 20 different health states. Each health state represented a subgroup of people that stopped treatment based on time on treatment, up to 20 years. Each of these states separately modelled the discontinuation events (proportion of people with manifestations and treatment use) for people stopping treatment in the first 20 years. The EAG confirmed that these treatment discontinuation groups had been implemented correctly. The committee concluded that the revised model was acceptable for decision making.

Lifelong treatment effect

3.10 In the company's economic model, it assumed that the benefits of leniolisib would remain the same over a lifetime of taking the treatment. The EAG's clinical experts highlighted that there was no long-term data beyond 6 years to support or refute the assumption of sustained efficacy over time. The company explained that:

- The mechanism of action of leniolisib means that the treatment effect is not expected to diminish over time. This is because there is no clear mechanism for APDS to develop resistance to leniolisib. This was supported by the company's clinical experts. The clinical experts at the committee meeting stated that they could not predict the long-term effectiveness of leniolisib without more data. They added that they do not know whether other inhibitor drugs in similar disease areas had shown any waning of treatment effect. Waning is sometimes seen in oncology, although that mechanism of waning is not relevant to this evaluation. But, they noted that theoretically, if antibodies are not made, then they could not see how treatment effect waning could occur.

- APDS is not caused by any other mechanism. This means that while the activity of the PI3K delta pathway is normalised by leniolisib, APDS cannot continue to progress. This was supported by the clinical experts.

  Data from the 2201 clinical trials and the EAP (up to 6 years) showed that there was no loss of efficacy or waning of effect. For this reason, the company stated that the only way that the effects of leniolisib could be lost would be by poor adherence or by stopping treatment. The company noted that in UK and US studies of leniolisib, there has been very high adherence (99%). Based on this, and because symptoms may return rapidly for people who are less adherent but continue to take treatment, the company expected high adherence to leniolisib in the long term. The committee noted that high adherence is common in clinical trials. But it was also aware that leniolisib would be the first pathway-specific treatment option available for this rare condition, so adherence would likely remain high in clinical practice. The EAG was concerned that the high adherence assumed by the company may be an overestimation and stated that treatment waning needed to be explored in the model. But it did note the difficulty of including this given the lack of available data.

  To investigate a waning treatment effect using a proxy, the EAG increased the discontinuation rate from 3.54% (assumed by the company in its base case at the first committee meeting, see section 3.11) to 14%. The EAG highlighted that a significant limitation of its exploratory analysis was that it stopped the accrual of leniolisib costs and benefits, which did not accurately

reflect what would happen if the treatment effect did wane.

A preferable approach would be to model a declining treatment effect while the cost of leniolisib was still accrued. The EAG noted that this had not been tested because there was a lack of data about how leniolisib's treatment effect would wane over time. The committee acknowledged the data limitations, but thought that applying a discontinuation rate to account for a waning of leniolisib effect was not appropriate. It noted that it would have liked to have seen treatment waning explored with alternative methods. The committee noted that without longer-term data, there was uncertainty about whether the benefits of leniolisib while on treatment would be sustained. It concluded that based on the mechanism of action, it was plausible, but it would consider the uncertainty around a sustained lifelong effect of treatment in its decision making.

Treatment discontinuation

Treatment discontinuation rate

3.11 In the company's base case, it assumed that 3.54% of people in the leniolisib arm stopped treatment each year. This was based on the discontinuation data from Study 2201E1 and the EAP. During an expert elicitation exercise, the company asked 5 clinical experts what proportion of people it expected to stop treatment at any point and for any reason. The mean estimated response was 14% and the potential reasons for stopping treatment included patient choice, adverse events and lack of adherence. The EAG used the mean estimate (14%) as its discontinuation rate per year. The committee questioned the timeframe around the elicited discontinuation rates, whether these were annual rates, or lifetime rates, noting that 14% stopping treatment each year was high. It thought that 3.54% appeared a more realistic assumption.

In response to consultation, the company updated the model discontinuation rate to 2.7% per year. This was to reflect the latest Study 2201 and EAP data (November 2024). The EAG and clinical experts agreed that this was the most appropriate data to use. The committee concluded that a discontinuation rate of

2.7% per year was the most appropriate rate to use.

Clinical plausibility of manifestations and treatment use after stopping leniolisib

3.12 In the first committee meeting, the company noted that there was uncertainty about how the rate of manifestations and standard treatment use would change after people stopped taking leniolisib. It highlighted that there was no real-world evidence available, but that a small proportion of people (n=6) took a break from treatment during the clinical trials. For these 6 people, who had an average treatment gap of 233 days, there was evidence that immunoglobulin levels and spleen size increased and naive B cells decreased when leniolisib treatment was stopped. After restarting leniolisib treatment, these measures began to improve again. The company acknowledged that after stopping leniolisib treatment, people will have an increased risk of manifestations and mortality, and be more likely to use other treatments. The clinical experts explained that while on treatment with leniolisib, the disease process is stopped because the PI3K delta pathway is no longer overactive, preventing exhaustion of the immune system. This means that it can repopulate with immature white blood cells, which can then develop normally to become mature white blood cells. The longer that someone is on treatment, the longer the immune system has to recover.

The company believed that for people who stop treatment but whose immune system has had time to recover fully, manifestations and treatment use would return as if the APDS was progressing from birth. For example, the first manifestation may appear around 2 years after stopping treatment (see section 3.2). The clinical experts explained that this may not be clinically plausible, for example, babies are at a greater risk of infections than older people because of the development of the immune system and immunity over time. So, a 30-year-old coming off treatment is less likely to develop infections than a newborn. The company added that the rate of symptoms returning is a function of both the condition of the person when they started treatment and how long they were on treatment. For example, if someone stopped treatment soon after starting, it would not take long for their manifestations to return. One clinical expert highlighted that they would expect a relatively quick relapse of symptoms, potentially after a period of months or years, but not decades. This was based on

their experience of using a similar type of pathway-specific drug for another disease. The clinical experts also explained that not all manifestations would return at the same rate, and preventing different manifestations would have different long-term effects. For example, infection-based manifestations would likely return quickly, but preventing them at an earlier age could have long-term benefits. But, immune dysregulation manifestations such as lung disease and lymphoma would not reappear straight away.

During consultation, the company asked 6 UK APDS clinical experts about the expected return of manifestations and treatment use for people who stop leniolisib. The clinical experts thought it was most clinically plausible for people to return to the same risks they had before starting leniolisib, regardless of the age at discontinuation and time on treatment. They added that while on treatment, leniolisib would most likely stop the development of manifestations, but that people will be at risk again after stopping treatment. Some experts agreed that the rate of return could be related to how long someone had been on treatment, with the longer the time on treatment, the less likely it was that manifestations would return. But they did not think it was plausible for:

- there to be a lower risk after stopping treatment in older people
- the risk to immediately return to standard care rates
- the risk to be higher than for people on standard care, or
- people who had had treatment for 10 or more years to return to standard care rates.

The committee understood that how quickly manifestations and treatment use would return to the standard care rate would depend on:

- how long someone had been having treatment
- the type of manifestation, and
- potentially, the age at which they started treatment.

Modelling returning manifestations and treatment use

3.13 For the first committee meeting, the company assumed a constant linear increase for each manifestation and treatment use, until they returned to the rates seen in standard care. It noted that the assumption of a gradual return was more plausible than assuming the risks would immediately match the standard care arm. This is because time would be needed for the immune system to change after stopping treatment. The committee understood that how quickly manifestations and treatment use would return to the standard care rate would depend on several factors (see section 3.12). Considering this, it questioned whether this rate of return was being accurately represented in the model. For example, an extreme scenario was tested that assumed a 100% discontinuation rate after 1 year. In this scenario, the rate of return to standard care levels appeared to take many years and some of the benefits of leniolisib were sustained for a lifetime. This resulted in an incremental gain of 2.36 quality-adjusted life years (QALYs). The committee thought that this lacked face validity. The company stated that the structure of the model using the cohort data meant that the model did not allow these types of assumptions to be explored, so the scenario would not be accurate. The committee also questioned whether discontinuation had been implemented correctly in the model and asked for the modelling to be checked by a statistician. It also asked for the rate of return of manifestations to be checked for plausibility. This was because testing this assumption in the model suggested that the benefit of leniolisib was being overestimated after treatment was stopped. The committee suggested this could be modelled so that the probability of developing a manifestation each year after stopping treatment followed the hazard rate of the cumulative incidence functions from age 0 (for example a 20-year-old stopping treatment would revert to the hazard of each manifestation of a newborn). Additional scenarios could also be presented, such as:

- adjusting the hazard rate of infections to reflect lower risks in older people
- adjusting hazards for duration of treatment
- a conservative scenario modelling an immediate return to standard care rates of manifestations and treatment use.

In the first committee meeting, the committee concluded that further work was needed to ensure the rate of return of manifestations and treatment use

was being modelled appropriately.

Updated modelling of returning manifestations and treatment use

3.14 In response to consultation, the company presented a revised model to address some of the committee's concerns about the modelling of leniolisib discontinuation (see section 3.9 and section 3.13). This allowed the company to apply different annual-specific risks to groups depending on how long they had had treatment with leniolisib before stopping treatment. The EAG confirmed that discontinuation had been implemented correctly in the revised model. It noted that there were a few errors in the cumulative incidence calculations of infections after stopping leniolisib. But these were not expected to have a substantial impact on the results. There was also some uncertainty about how the manifestation hazard ratios were calculated in the model.

The company considered the advice from the 6 UK APDS clinical experts (see section 3.12) and used this to explore alternative post-discontinuation manifestation risks and treatment use:

- Base case: return to standard care risks equal to the risk at the start of treatment with leniolisib. For example, if treatment had been started at age 15, risks would return to that of a 15-year-old after treatment had stopped.
- Scenario 1: return to standard care risks equal to the risk at the age at discontinuation. For example, if treatment stopped at age 20, in the next 1-year model cycle, the person would return to the risks of a 21-year-old.
- Scenario 2: return to risks of a newborn for long-term manifestations (bronchiectasis, advanced lung disease and malignancy) and to standard care risks equal to the risk at the age of discontinuation for the remaining manifestations and treatment use.
- Scenario 3: return to standard care lifetime risk by applying a catch-up function equal to the time on treatment. For example, if treatment was stopped within the first year, the risk would return to the standard care lifetime risk within 1 year of discontinuation. This temporarily applied risks

higher than risks in the standard care arm to the leniolisib post-discontinuation arm. People who stopped leniolisib after 10 or more years would return to the same risk experienced before starting leniolisib (same as the base case).

The EAG thought that the approaches taken to model discontinuation were generally appropriate. It noted that the face validity concerns identified in the first committee meeting persisted when exploring some alternative returning rate model assumptions (see section 3.13). But it explained that this was related to the assumptions made about returning rates and disutility values, rather than errors in the model. The EAG was unable to obtain any additional clinical expert opinion during consultation, so based on the clinical evidence available, it agreed that returning to the same risk before leniolisib was started (company base case) was most appropriate. The clinical experts at the committee meeting also agreed that the base-case approach seemed most plausible, but highlighted that the data to accurately inform this was not yet available. The committee questioned if, using the base-case approach, people that stopped leniolisib would ever catch up to the standard care rate, or if some treatment benefits would be maintained for a lifetime. The clinical experts noted that this would depend on how long someone was on treatment. They explained that treatment for up to 5 years was unlikely to prevent someone's risk of manifestations returning to the standard care risk. But treatment for 10 years could be sufficient to cause a meaningful change in immunity and potentially allow someone to return to a lower risk than when they started treatment. The clinical experts also highlighted that the age at which treatment was started could affect leniolisib's impact. The committee considered that the base case was the preferred approach of the company, EAG and clinical experts. It noted that this method may not account for the potentially lower risks that people having treatment for a long time before discontinuation may have. But it also did not account for the quick return to standard care rates for people who stop treatment early. On balance, the committee concluded that the base case was the most appropriate approach presented to model the return to manifestations and treatment use after stopping leniolisib.

Survival modelling

3.15 For the first committee meeting, the company had modelled standard care survival by fitting a Weibull distribution to published APDS case series survival data. It used a hazard ratio to calculate survival in the leniolisib arm (the exact value is confidential and cannot be reported here). For the second committee meeting, the company had updated its source of standard care survival data to the latest ESID registry data (November 2024). It said that the latest data indicated that standard care survival had previously been overestimated. Leniolisib survival was also updated in response to clinical expert advice that suggested that people whose APDS responds to leniolisib would be expected to have similar survival to the general population. So, the company applied a relative risk of survival for leniolisib versus the general population (the exact value is confidential and cannot be reported here). The EAG noted that the company base case used APDS-specific mortality rates and that mortality in the model was not linked to manifestations. It stated that people with more manifestations would have a higher mortality rate and that any scenario that changed the risk of manifestations should also affect survival predictions (see section 3.14). It added that the mortality rate associated with manifestations may also vary with age and the time of diagnosis. The EAG explored the impact of using manifestation-specific mortality rates in the model. It found that the leniolisib survival curve did not vary significantly as the manifestation risks changed. The EAG highlighted that these scenarios were associated with substantial limitations and uncertainties because there was not sufficient data available to model the association between manifestations and mortality accurately. So, the EAG preferred to use the APDS-specific manifestation rate in its base case. The committee acknowledged the attempt to model mortality taking into account manifestations. But it agreed that the data was not currently available to model this accurately. The committee concluded that an APDS-specific mortality rate was the most appropriate to use.

Emotional benefits of leniolisib

3.16 The company believed that in addition to reduced manifestations and standard treatment use, leniolisib also reduced the emotional burden felt by people with APDS. This was a result of having a lower expected risk of developing

manifestations, having a reduced mortality risk and having increased hope because of the availability of a new treatment. The company thought these factors would improve the overall wellbeing of people having leniolisib, including increased vitality, reduced anxiety, and improvements in manifestations not captured in the model. The patient and clinical experts supported this, noting that the APDS community has felt increased hope with the potential availability of the first pathway-specific treatment. To account for these positive effects of leniolisib, the company applied an additional treatment-related utility gain of 0.1 to the leniolisib arm in the model.

The EAG acknowledged that leniolisib may have positive effects on the emotional state of people with APDS, which could affect health-related quality of life. But it stated that there was insufficient evidence presented to quantify this additional utility impact. The company explained that patient narratives collected during the Study 2201 trials reported improvements in energy, future outlook and manifestations not captured in the model. This meant that the modelled potential benefits of leniolisib may have been underestimated. The company provided evidence from 3 studies that had quantified the impact of a positive view, optimism and reduced anxiety on quality of life using the EQ-5D. The studies showed a utility gain of between 0.11 and 0.17. The company anticipated that leniolisib's quality-of-life benefits would extend beyond these factors. The EAG was concerned about the validity of the utility gain and the generalisability of these values to people in the UK with APDS. It highlighted that many of the utility values in the model were derived using the EQ-5D, which already contains an anxiety and depression dimension. So, including an additional psychological impact may result in double counting. The EAG thought that the evidence supporting the emotional utility gain was uncertain and was likely to bias the cost-effectiveness results, so it removed it from its base case. It suggested that further evidence on the utility impact of reduced emotional burden from leniolisib would help to evaluate the validity of this assumption. The committee thought that leniolisib could improve the emotional state of people with APDS and their families. But it was mindful that treatments should be compared equally and that many new and existing treatments provide increased hope to people. The committee agreed that it had not seen enough evidence that the modelled utility values did not capture hope to suggest that it should be considered independently from effectiveness for APDS. So, it concluded that the additional utility gain should be removed from the model. For the second committee

meeting, the company removed the utility gain from its revised base case.

Non-reference case discount rate

3.17 The company believed that leniolisib met the criteria for the non-reference case discount rate of 1.5%. In its base case, it applied a 1.5% discount rate to health effects and a 3.5% discount rate to costs (differential discounting). This is because it expected treatment with leniolisib to begin at an early age (12 years, see section 2.1), so applying the 1.5% discount rate to health effects avoided the large reduction in the value of long-term health benefits. The committee noted that all of the following criteria in section 4.5.3 of the NICE health technology evaluations manual must be met for a 1.5% discount rate to be used:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

The committee also noted that the NICE health technology evaluations manual states that the 1.5% discount rate should be applied to both costs and health effects, so the differential discounting was not appropriate. It also thought that a discount rate of 1.5% should not be used for health benefits and costs. This was because evidence presented from case reports and patient narratives from the clinical trial stated that some manifestations improve, but do not fully resolve with leniolisib. Also, leniolisib did not reverse or improve existing damage caused by previous manifestations, such as lung scarring from infections. The model also assumed that people who remain on leniolisib still have manifestations, although they can be less severe. In addition, although the committee concluded that APDS does substantially reduce quality and length of life, there was uncertainty about the extent of this for all people with APDS because of the heterogeneity of the condition (see section 3.2). At the first meeting, the committee concluded that only criterion 3 had been met (see section 3.10). So, it concluded that a discount rate of 3.5% should be used for both health benefits and costs.

In response to consultation, the company provided additional evidence to support using a 1.5% discount rate for both costs and health benefits. For criterion 1, the company acknowledged that APDS presents as heterogeneous, because familial testing can diagnose APDS before symptoms occur in a minority of people. But it highlighted that UK data suggests that there is around a 7-year delay between the mean age of the first APDS symptom (2 years) and the median age of diagnosis (9 years). By age 10, more than 90% of people with APDS have had a manifestation that severely impacts quality of life, so only a minority of people diagnosed will not have had a manifestation. The clinical experts reiterated that a late diagnosis does not always mean that a person's life has not been impaired by APDS, noting that many people will have been misdiagnosed or have not yet had a diagnosis for their symptoms (see section 3.2). The company also stated that regardless of severity at diagnosis, APDS progresses in all people to cause a significantly reduced quality of life and life expectancy. For example, by age 46, 63% of people with APDS have had at least 1 severe manifestation (defined as malignancy or advanced lung disease) and ESID registry data shows a median survival of 44 years (see section 3.1). The company's clinical experts advised that APDS mortality is significantly underreported and that published literature likely overestimates survival. The committee considered the evidence presented and concluded that criterion 1 was met.

For criterion 2, the company emphasised that real-world evidence suggests that leniolisib is expected to remove the impact of manifestations, which would restore most people with APDS to full or near-full health. For example, it allows even people with the most severe APDS to return to school and work, improves quality of life and minimises the development of severe manifestations. The company acknowledged that although some organ damage from APDS is irreversible, the lack of further progression and the resolution of reversible aspects of APDS offers huge quality-of-life improvements. The clinical experts highlighted that it is not possible to reverse the existing damage caused by some manifestations. For example, although leniolisib may improve a person's immune system, it will not be able to reverse the existing structural damage from bronchiectasis. They explained that if in future APDS is diagnosed early in childhood, there could the opportunity to restore people to full health. The committee

acknowledged the potential for leniolisib to restore people to full or near-full health in a younger population. But it recalled that currently in the UK, at the time of diagnosis, most people in the licensed population (aged 12 years and over, see section 2.1) would have had a severe manifestation that would likely have caused irreversible damage. So it agreed that criterion 2 had not been met. The committee concluded that a discount rate of 3.5% should be used for both health benefits and costs.

Model uncertainty

3.18 The company explored the uncertainty in the model input parameters by running a probabilistic sensitivity analysis. For parameters that did not have a measure of uncertainty available, the company assumed a standard error of 10% of the parameter's mean. It noted a previous review of NICE single technology appraisals published between 2013 and 2014. The review found that 68% of appraisals had at least 1 parameter in the model for which the variation in the point estimate was assumed and not informed by data. In these cases, the standard error used was between 10% and 30%, with 20% being used most commonly. The EAG stated that using a 10% standard error was not justified. It explained that 10% was the lower bound of the range found, which suggests a high level of precision and certainty in the parameter point estimates. Given that many estimates used in the model were not based on directly relevant empirical evidence, it said this assumption did not seem appropriate. The EAG also highlighted that this assumption was applied to a large proportion of parameters, including key model inputs for utilities, costs and manifestation rates. The EAG noted that the impact on the cost-effectiveness estimates of using either a 10% or 20% standard error was small, but it considered a more conversative approach to be more appropriate. So it used a standard error of 20% of the mean in its base case. The committee thought that a 10% standard error was reasonable, but was mindful that it was applied to a large number of parameters in the model. It was concerned that the difference between the probabilistic and deterministic cost-effectiveness estimates was large, because this can sometimes indicate errors in the model. But it acknowledged that because the model was non-linear, the characterisation of uncertainty may affect the point estimate of the incremental cost-effectiveness ratio (ICER). In response to consultation, the company altered

the model structure (see section 3.9) and corrected some errors it had found. It noted that after this, the probabilistic and deterministic cost-effectiveness results of the revised base case were similar. The EAG agreed that the original difference in results had now been resolved. The committee concluded that its concerns about the probabilistic results were resolved.

QALY weighting

3.19 The committee understood that the NICE health technology evaluations manual specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take into account the size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee noted that the company's and EAG's deterministic and probabilistic base-case analyses showed QALY gains within this range. The size of the undiscounted QALY gains using the committee's preferred assumptions (see section 3.22) was 17.96. So the committee agreed that a QALY weighting of 1.796 should be applied.

Other factors

Equality

3.20 The committee considered that some people aged 12 years and over with APDS may have fewer suitable donors available for a haematopoietic stem cell transplant if they are from an ethnic minority background. It considered if the recommendation may have a greater impact on people from ethnic minority backgrounds. The clinical experts explained that a very limited number of people with APDS aged 12 years and over are offered a haematopoietic stem cell transplant because of the associated risks, and because these risks increase with

age (see section 3.4). Because use of haematopoietic stem cell transplants was very low in the older APDS population, the committee agreed that this was not an equality issue that could be addressed in this evaluation.

Uncaptured benefits

3.21 The committee considered whether there were any uncaptured benefits of leniolisib. It understood that leniolisib can improve manifestations associated with APDS, which can reduce the disease burden, emotional distress and social isolation reported by people with APDS. This could reduce the physical and emotional support needed from caregivers. This may reduce the stress reported by many carers (see section 3.3) and improve their quality of life. Leniolisib may also allow people with APDS and their carers to return to education and work. The committee thought that the additional benefits of leniolisib to people with APDS and their carers were not captured in the economic modelling. So it concluded that it would consider these uncaptured benefits qualitatively in its decision making by accepting a higher level of uncertainty in the clinical evidence and modelling assumptions than would normally be accepted (see section 3.8, section 3.10, and sections 3.14 and 3.15).

Cost-effectiveness estimates

Committee's preferred assumptions and cost-effectiveness estimate

3.22 The company and EAG revised base cases differed by 1 key assumption: the application of non-reference case discount rate (see section 3.17). The committee's preferred assumptions for the cost-effectiveness modelling of leniolisib compared with current clinical management were to:

- assume the benefits of leniolisib were sustained for a lifetime (see section 3.10)
- apply a 2.7% per year discontinuation rate (see section 3.11)

- return to the manifestation and treatment use risks at leniolisib initiation after stopping treatment (see section 3.14)
- model survival with an APDS-specific mortality rate using the ESID registry data (see section 3.15)
- exclude the emotional utility gain (see section 3.16)
- use a 3.5% discount rate for health effects and costs (see section 3.17)
- use a standard error of 10% of the mean for model inputs without uncertainty information available (see section 3.18).

The committee's preferred modelling assumptions aligned with the EAG's base case. The committee decided that a 1.796 QALY weighting should be applied (see section 3.19). It recalled that there was still a high level of uncertainty in some of the clinical evidence and modelling assumptions, but agreed that it would accept a higher level of uncertainty to account for the uncaptured benefits identified (see section 3.21). Using the committee's preferred assumptions, the cost-effectiveness estimates were within the range considered an acceptable use of NHS resources.

Conclusion

Recommendation

3.23 The committee agreed that its preferred cost-effectiveness estimate was within the range considered an acceptable use of NHS resources. So it recommended leniolisib for treating APDS in people aged 12 years and over.

4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Section 4f of The Innovative Medicines Fund Principles states that a discretionary source of early funding (from the overall Innovative Medicines Fund budget) is available for certain medicines recommended by NICE. In this instance, interim funding has been agreed for leniolisib. Interim funding is available from 28 March 2025 and will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has activated phosphoinositide 3-kinase delta syndrome (APDS) and the healthcare professional responsible for their care thinks that leniolisib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical, a project manager and an associate director.

Cara Gibbons
Technical lead

Caron Jones and Christian Griffiths
Technical advisers

Celia Mayers and Leena Issa

Project managers

Lorna Dunning
Associate director

6 Update information

October 2025: In section 2, the list price for leniolisib was updated.

ISBN: 978-1-4731-6939-5