# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using leniolisib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

**This document has been prepared for consultation with the stakeholders.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?



Issue date: October 2024

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using leniolisib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 21st November 2024
- Second evaluation committee meeting: 11th December 2024
- Details of the evaluation committee are given in section 4

# 1 Recommendations

1.1 Leniolisib is not recommended, within its marketing authorisation, for treating activated phosphoinositide 3-kinase delta syndrome (APDS) in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with leniolisib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

**Why the committee made these recommendations**

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 cause 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.

There are uncertainties in the economic modelling around how best to model the effect of stopping treatment.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for leniolisib. So it is not 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

2.4 The list price for leniolisib is commercial in confidence.

2.5 The company has a commercial arrangement, which would have applied if the leniolisib had been recommended.

# 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%), 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 survival studies estimating that 68% of people with APDS are alive at age 40 years. The committee considered 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, most people have manifestations within the first 2 years of life, but the median age of diagnosis is around 12 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 an asymptomatic condition that is only diagnosed 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

ADPS'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. But with increased reporting, the heterogeneity will also increase. The committee considered 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 for 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 genetically 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. 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. Current 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 hematopoietic stem cell transplants are mainly reserved for children with APDS and very few people aged 12 years and older 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 individual and that a person's 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 where 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 people with APDS (see section 3.2), describing how they have to offer personalised treatments, even within families, because the presentation of APDS can be so different. 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 considered 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 in the interim period if leniolisib was recommended before the licence was extended, 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 considered that people who weigh less than 45 kg may have access to leniolisib off-label. But it concluded that because this weight is outside of the current dosing recommendations, they would not be included within 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 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 indicates 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 and to inform the economic model (see section 3.6). This included data from:

- European Society for Immunodeficiencies (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 ESID analyses 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. 21 physicians completed questionnaires on behalf of 30

out of the 40 individuals 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 is 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 was generally reflective of 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 a very 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 the Study 2201 part 2 trial 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

those 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 horizon. The benefits of leniolisib were modelled by the resolution or reduced incidence and severity of manifestations and treatment use. The committee considered that use of a treatment-state model rather than a health-state model had created some complexities in the modelling of the leniolisib treatment effect (see sections 3.10 and 3.11). 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 3.11). The committee concluded that it would have preferred to see a health-state model that could be fully explored.

## 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 people 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. Waning is sometimes seen in oncology, although the 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.

  Up to 6 years of data from the 2201 clinical trials and the EAP showed that there was no loss of efficacy or waning of effect. For this reason, it stated that the only way that the effects of leniolisib could be lost is 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 acknowledged 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.

As a method to proxy a waning treatment effect, the EAG increased the discontinuation rate from 3.54% (assumed by the company in its base case, 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 considered that applying a discontinuation rate to account for 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 considered 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 this uncertainty in its decision making.

### Treatment discontinuation

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 considered that 3.54% appeared a more realistic assumption.

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. To implement this in the model, it assumed a constant linear increase for each manifestation and treatment use, until they returned to the rates seen in standard care. The company 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 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 noted 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 noted 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 in another disease area. 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.

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

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

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 the model. In this scenario, the rate of return back to standard care

appeared to take many years and some 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 considered 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 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 that the modelling 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. It suggested this could be modelled so that the probability of developing a manifestation each year after stopping treatment follows the hazard rate of the cumulative incidence functions from age 0 (for example a 20-year-old discontinuing reverts to the hazard of each manifestation of a newborn). Additional scenarios could also be presented, such as:

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

The committee concluded that a 3.54% discontinuation rate seemed the most plausible rate to model, but further work was needed to ensure the rate of return of manifestations and treatment use was being modelled appropriately.

## Emotional benefits of leniolisib

3.12 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 treated with 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 have 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 about the quantification of 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 considered 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 with APDS. The committee considered that it had not seen enough evidence that the modelled utility values did not capture hope, suggesting that it should be considered independently from effectiveness for APDS. So, it concluded that the additional utility gain should be removed from the model.

## Non-reference case discount rate

3.13 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 from 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 it noted that differential discounting was not appropriate. It also thought that a discount rate of 1.5% should not be used for both 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). So, the committee concluded that a discount rate of 3.5% should be used for both health benefits and costs.

## Model uncertainty

3.14 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 assumed 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 that there is 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 considered 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). The committee concluded that it would like to know what factors were driving the difference between the deterministic and probabilistic cost-effectiveness estimates.

## QALY weighting

### Criteria for applying a QALY weighting

3.15 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 account of 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 some of the company's analyses showed QALY gains within this range, but that the EAG's analyses did not. Because there were uncertainties remaining about the benefits of leniolisib after stopping treatment (see section 3.11), there were also uncertainties in the QALY gain estimates. So the committee was unable to conclude whether a QALY weight was appropriate to apply without further information.

## Cost-effectiveness estimates

### Company and EAG cost-effectiveness assumptions

3.16 The company and EAG base case differed by 5 key assumptions:

- lifelong treatment effect (see section 3.10)
- discontinuation rate (see section 3.11)
- application of an emotional benefit utility gain (see section 3.12)
- application of non-reference case discount rate (see section 3.13)
- the standard error used to model uncertainty in parameters without available uncertainty information (see section 3.14).

### Company's preferred cost-effectiveness estimate

3.17 The committee concluded that its 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 3.54% per year discontinuation rate (see section 3.11)
- exclude the emotional utility gain (see section 3.12)
- use 3.5% discount rate to health effects and costs (see section 3.13)
- use a standard error of 10% of the mean for model inputs without uncertainty information available (see section 3.14).

The committee recalled that there remained a high level of uncertainty in some of the modelling assumptions. It considered that it could not establish its preferred cost-effectiveness estimate, QALY weight or acceptable ICER until it had been presented with further analyses. It noted that the company should explore the following in the modelling:

- whether stopping treatment with leniolisib was modelled accurately and alternative scenarios around the return of manifestations and treatment use rates was plausible (see section 3.11)
- what drove the difference between the probabilistic and deterministic cost-effectiveness estimates (see section 3.14).

# Other factors

## Equality

3.18 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 appraisal.

## Uncaptured benefits

3.19 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 physical and emotional support needed from caregivers. This may reduce the stress reported by many carers (see section 3.3) and improve their health-related quality of life. The committee considered that the additional benefits of leniolisib to caregivers of people with APDS were not captured in the economic modelling. So it concluded that it would consider caregiver quality of life qualitatively in its decision making by accepting a higher level of uncertainty in the clinical evidence (see section 3.8).

# Conclusion

## Recommendation

3.20 The committee recalled the uncertainties in the company's modelling and cost-effectiveness estimates. It considered that more exploration of the modelling of treatment discontinuation and the difference between the probabilistic and deterministic cost-effectiveness results was needed

before a decision could be made about the most appropriate cost-effectiveness estimate. So it did not recommend leniolisib for treating APDS in people aged 12 years and over.

# 4 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**

Project manager

**Lorna Dunning**

Associate director

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