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

For committee – contains no confidential information

Technology appraisal committee HST [10 October 2024]

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Leniolisib for APDS in people 12 years and over

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on APDS [1]

APDS diagram

People with APDS are unable to fight infections because their immune system does not work properly

What is APDS?

- An ultra-rare condition first recognised as a unique disease in 2013, characterised by both immune dysregulation and immune deficiency

Causes

- An overactive enzyme (a protein called P13K delta) from mutations in APDS-relevant genes
- P13K delta protein plays an important role in how cells develop and mature
- People with APDS therefore may produce too few of some types of white blood cells and/or too many of others e.g., B and T cells, and as a result, the immune system cannot work correctly
- This leads to frequent infections, lung disease, inflammatory bowel disease and, in severe cases, malignancies
- 2 types of APDS = APDS1 (results from mutation of gene encoding catalytic subunit of P13K delta) and APDS2 (associated with mutation of gene encoding the regulatory subunit of P13K delta)

Epidemiology

- Mutations causing APDS can either be inherited or develop randomly, and occur regardless of sex and ethnicity
- Between 1-2 people out of every 1 million live with APDS. In England, between 40 to 50 people have APDS

Diagnosis

- APDS population is very heterogeneous, with large variation in diagnosis age, symptoms and severity
  - ↳ Most people manifest within 2 years of life but UKPID registry median age at APDS diagnosis is 12 years

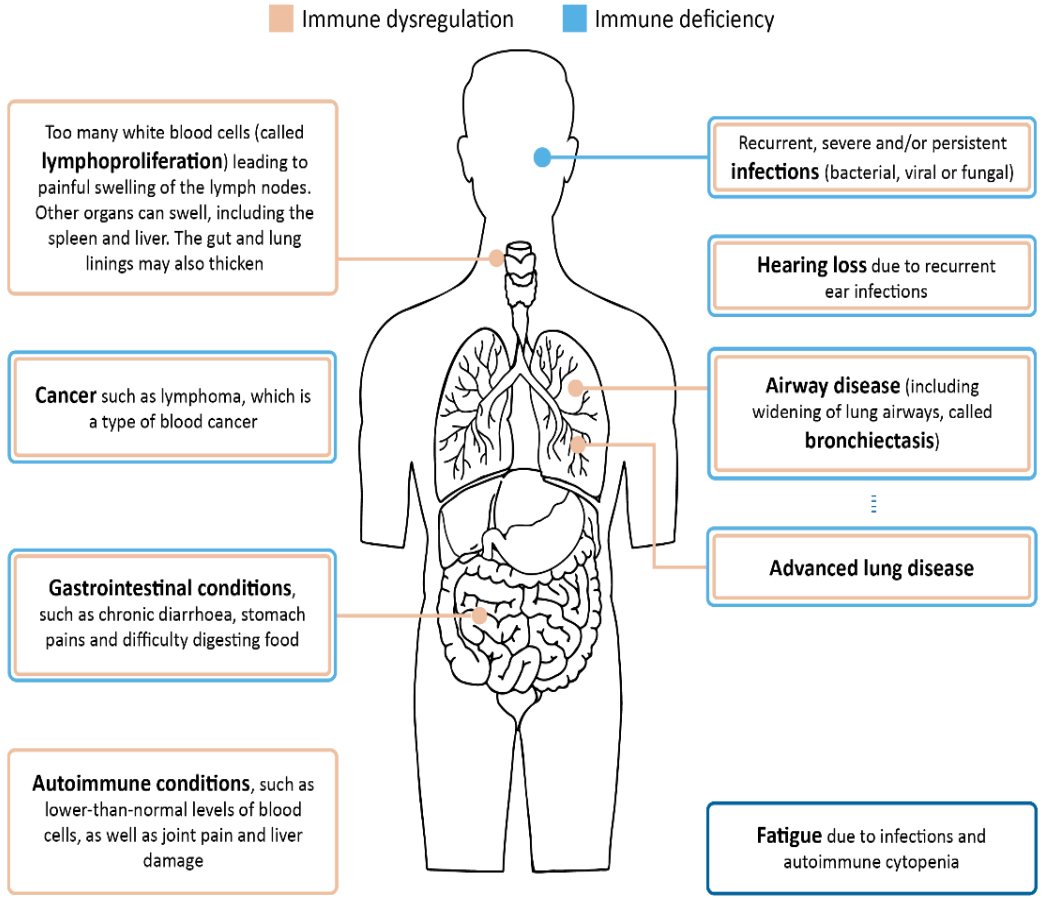
Abbreviation: APDS, activated phosphoinositide 3-kinase delta syndrome; UKPID, UK Primary Immunodeficiency Registry

Background on APDS [2]

APDS manifestations

- APDS varies on an individual level, affecting people to different extents:
  - People may have multiple severe manifestations which severely impact QoL and significantly shortened life
  - Others may be asymptomatic and not know they have APDS until a relative is diagnosed
- Two main ways immune system no longer works correctly:
  1) immune dysregulation - causes specific organs to swell, or leads to autoimmunity (immune system attacks body's own healthy tissues or organs)
  2) immune deficiency - body does not effectively fight abnormally growing and/or infected cells e.g., bacteria / viruses, which can cause infections

Manifestations of immune dysregulation and immune deficiency



How does APDS progress over time?

- Disease onset can be variable over time in terms of age at presentation and complications
- Manifestations often start in early childhood → by ages 5 and 10, ~70% and 90% have had manifestations
- As people age, the disease progresses, and people have more manifestations which can be more severe
  - This can lead to irreversible end-organ damage and lymphoma → by age 40, ~78% have lymphoma
- APDS manifestations often lead to premature death, survival studies estimate 68% alive at age 40

Abbreviation: APDS, activated phosphoinositide 3-kinase delta syndrome; QoL, quality of life

Leniolisib (Joenja®, Pharming)

Marketing authorisation	• **Indication (granted September 2024):** for the treatment of activated phosphoinositide 3-kinase delta (P13Kδ) syndrome (APDS) in adult and paediatric patients 12 years of age and older • Followed International Recognition Procedure.
Mechanism of action	• Leniolisib is a P13K delta inhibitor that specifically lowers the activity of P13K delta (i.e. reduces its ability to send signals), normalising P13K delta signalling. By fixing the overactive enzyme, this allows white blood cells to develop properly and to fight infection more successfully.
Administration	• 70 mg, twice daily (12 hours apart), administered orally • SmPC: no recommended dosage for people weighing less than 45 kg
Testing	• Genetic testing for APDS is already available and is standard practice in NHS
Price	• List price is pack of 60 tablets: [redacted] • A patient access scheme is applicable

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Abbreviations: APDS, activated phosphoinositide 3-kinase delta syndrome; SmPC, summary of product characteristics

Patient perspectives [1]

Survey summary statistics

Immunodeficiency UK and NICE ran survey to help understand impact of APDS on patients and carers

Submissions from Immunodeficiency UK and company's Summary of Information for Patients

APDS from the patient perspective

- APDS significantly impacts daily life, mental health, QoL and the ability to work, socialise, have hobbies and attend school
- Living with APDS can cause feelings of anxiety, stress and loss of hope, and people struggle to live normal lives – 31% reported satisfaction with QoL

"Growing up I didn't really think I'd make it very far, didn't plan for a lot of things in my future… because I didn't think I'd have a future to plan for"

- To avoid infections, people often make lifestyle adjustments such as social distancing, so are often unable to socialise, go to school or work, and have difficulties making and maintaining relationships
- Cancer has a particularly negative QoL impact for people with APDS, causing a lot of mental stress

"My mental health has been put to a hard test and…I'm going on fighting with permanent anxiety relevant to the fact that my body could let me down at any moment"

- Symptoms such as lung disease can make it hard for people to take part in hobbies and do everyday tasks, leading to feelings of frustration
- People feel "drained, both mentally and physically" from various manifestations, symptoms and frequent hospitalisations
- Symptoms reported to have an extreme impact: bronchiectasis, respiratory infections, chronic cough, infections, autoimmunity problems, enlarged lymph nodes and spleen, gastrointestinal problems, and hearing problems

"Makes me feel so down, depressed and isolated"

NICE

Abbreviations: APDS, activated phosphoinositide 3-kinase delta syndrome; QoL, quality of life

Patient perspectives [2]

Uncaptured benefits - carer QoL

Due to the severe and complex manifestations, many people with APDS require physical and emotional support from caregivers

APDS from the caregiver perspective

"[Patient] will wake up in the middle of the night crying out in pain"

- The stress of caring for people with APDS may have a negative impact on the emotional wellbeing of caregivers (for example, there have been reports of depression, anxiety and anger)
- Caregivers reported that their caring responsibilities affect their daily responsibilities e.g., reduce working hours to attend hospital appointments and/or manage medical issues
- APDS may impact wider family life, e.g., restrictions on family holidays due to concerns that certain destinations may have greater risks of infections and due to logistical difficulties e.g., working around treatment schedules.
- Caregiving responsibilities negative impact relationships with loved ones, due to low moods or lack of time

"We don't get together with people like we used to, because either it's not exposing her to other stuff, we're too tired to or she just is not feeling up to it"

- 7/8 reported that APDS highly affected their family
- APDS has a significant impact on individuals and families in terms of time spent managing appointments and disruption to lives by time spent in hospital:
  - Over 12 months, average of 24.6 outpatient visits, 17.6 days in hospital
  - Some people reported 200+ outpatient visits and 80 days in hospital

"2-3 physio sessions a day, medicine administered daily, weekly infusions"

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Abbreviations: APDS, activated phosphoinositide 3-kinase delta syndrome; QoL, quality of life

Patient perspectives [3]

Current treatments do not treat the cause of APDS - leniolisib could be a bridging treatment to keep people fit enough to have HSCT, a potential of cure

Burden of treatment

"It's a medicalised life with regular blood tests, immunoglobulins replacement therapy"

- People with APDS face demanding treatment plans, including lengthy, regular hospital stays for invasive procedures which adds extra stress and upset to their daily schedule
- People can be taking multiple treatments → survey reported 2 people taking 6 medications
- Despite current treatments, not all symptoms are helped and still a high risk of lymphoma and death early in life

Leniolisib for APDS

"I feel like I took a life pill. I could breathe better and had more energy, and I could just do more things"

<u>Benefits</u>

- Overwhelming patient support for the availability of leniolisib for the treatment of APDS
- People reported benefits including a reduction in coughing, lymph node size, antibiotic use and hospital admissions and an increase in blood count, energy and appetite
- Benefits could translate into ability to have a full education and working life and improved quality of life

"I would recommend everyone with APDS to try this treatment as I have noticed slight improvement in my condition which has made me feel a little better"

<u>Drawbacks</u>

- Side effects e.g., mouth and tongue ulcers
- Did not tackle infection damage caused before taking leniolisib

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Abbreviations: APDS, activated phosphoinositide 3-kinase delta syndrome; HSCT, haematopoietic stem cell transplant

Clinical perspectives

Submission from Professor of Translational Immunology at University College London

- Please see committee papers for clinical expert submission.

NHS perspectives

APDS requires lifelong treatment and tends to worsen overtime as comorbidities accumulate

- No national guidance for the treatment of APDS, but care pathway to diagnosis is well defined
- Treatment approach depends on the patient's clinical features and people are usually treated collaboratively between centres with shared expertise → no significant variation between physicians across NHS
- Treatment approaches vary from supportive only, surveillance for malignancies, to pre-emptive HSCTs
- Treatments include prophylaxis with antimicrobials, immunoglobulin replacement, off-label mTOR inhibitors
- In theory, leniolisib could provide improved health and QoL rather than progressive deterioration
    - May reduce long-term healthcare resource use in people who respond e.g., reduced hospital attendance, acute service utilisation, stop need for ongoing IgG replacement
    - Would only be prescribed from accredited specialised immunology services (paediatric and adult)
    - Would be used to replace mTOR inhibitors and in good responders might displace need for HSCT
- Need investment for potentially homecare delivery of leniolisib for community dispensing
- Genetic testing for APDS is already part of standard care and routinely commissioned in the NHS

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Abbreviation: HSCT, haematopoietic stem cell transplant; QoL, quality of life; APDS, activated phosphoinositide 3-kinase delta syndrome, mTOR, mammalian target of rapamycin

Equality considerations

Equality issues raised by the company and stakeholders

Diagnosis and management of people with APDS

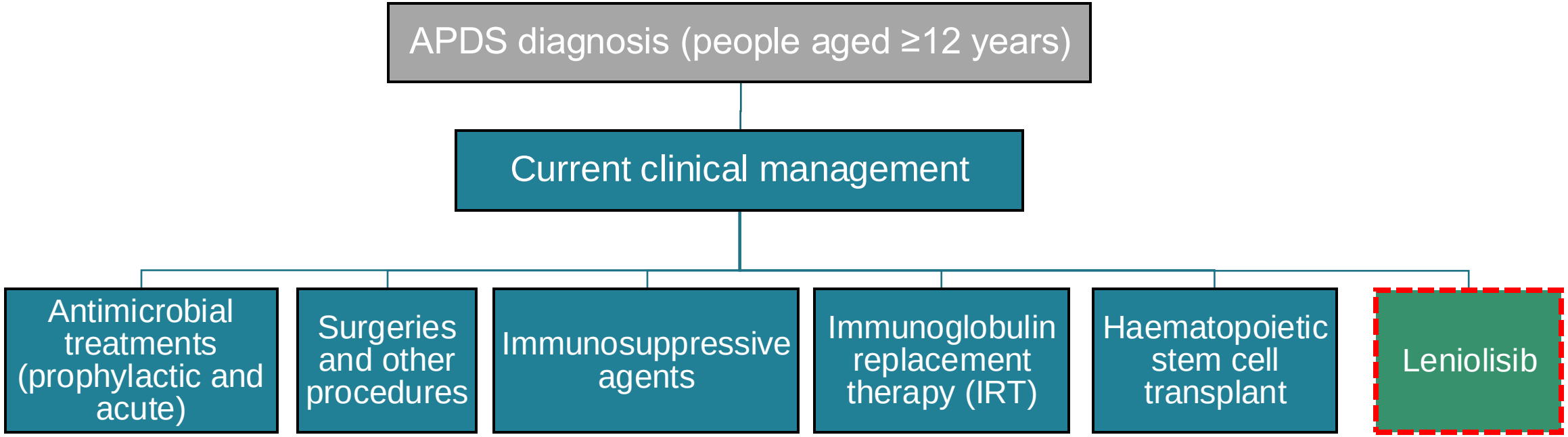
- Currently no licensed treatments available for APDS or UK clinical guidelines. This may lead to sub-optimal and inconsistent use of off-label medicines and variable approaches in managing APDS
- Variable manifestations may make it challenging to accurately recognise and diagnose APDS, leading to delayed diagnoses with a median delay of 7 years
- People with suspected APDS can be referred to up to 6 different clinicians during APDS diagnosis pathway
- Awareness of APDS in the medical community is still low and can compound diagnostic challenges
- Individuals living in areas not served by a specialist immunology service or for groups where referral to specialist services occur less frequently

Haemopoietic stem cell transplant availability

- For people being considered for HSCT, there are fewer suitable donors available for individuals from some ethnic minority backgrounds
- Leniolisib may reduce inequality by improving health of people who are unable to benefit from HSCT because of the lack of tissue-matched stem cell donors
- HSCT access may be restricted for some young people with APDS due to the lack of parental consent

Abbreviations: HSCT, haemopoietic stem cell transplant; APDS, activated phosphoinositide 3-kinase delta syndrome

Treatment pathway



- APDS population is very heterogeneous, with large variation in diagnosis age, symptoms and severity
- UK treatments for APDS are decided on a case-by-case basis and treat the symptoms, not the cause
- Currently, no licenced medicines for APDS are approved by marketing regulators in the UK
- Off-label mTOR inhibitors (such as sirolimus or everolimus) are also used to treat people with APDS

What is considered standard care for managing the symptoms of APDS in UK clinical practice? What treatments would be used alongside leniolisib?

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Abbreviations: APDS, activated phosphoinositide 3-kinase delta syndrome; mTOR, mammalian target of rapamycin

Decision problem

	Final scope	Company	EAG comments
Population	People with APDS 12 years of age and older	Same as scope • SmPC posology: no recommended dosage for people weighing less than 45KG • 2 ongoing paediatric trials (1-11 years) using lower doses for future MA extension based on weight	Generalisability concerns: • BNF: mean weight for 12-year-old is 39kg • Clinical trials: people required to weigh over 45kg • Dosing may exclude otherwise eligible adolescents
Intervention	Leniolisib		
Comparators	Established clinical management without leniolisib		
Outcomes	Infections, Lung function, Fatigue, Mortality, Disease severity, Immunophenotype measures, Immune system function, AE and serious AE, HRQoL	All outcomes presented • Mortality and lung function not pre-specified in trial but trial safety data available	Outcomes broadly match scope • Additional data provided for outcomes not in scope and inform model
Modelling	Reference case	PSS costs not modelled	No social care costs

Abbreviations: HRQoL, health-related quality of life; BNF, British National Formular; PSS, personal social services; AE, adverse events; SmPC, summary of product characteristics; MA, marketing authorisation

Key issues

Issue	ICER impact
Uncertainties in the key clinical trial ○ Clinical trial comparator arm excluded treatments used in current clinical management so may not be generalisable to UK practice ○ Baseline imbalances, novel surrogate primary endpoints, and small sample size	Unknown
Lifelong treatment effect assumed ○ Company assume that there is no waning of leniolisib effect for the duration of treatment	Large
Treatment discontinuation ○ Company model a slow return to standard care manifestation rates after stopping leniolisib	Large
Utility gain from emotional benefit ○ Company assume leniolisib reduces APDS emotional burden by lowering expected risk of developing manifestations, reducing mortality, and increasing hope due to new treatment	Large
1.5% non-reference case discount rate ○ Company applied a 1.5% discount rate to health effects and 3.5% discount rate to costs	Large
Model uncertainty – probabilistic sensitivity analysis ○ Company assume a standard error of 10% of mean for inputs with no uncertainty information ○ Large difference in cost-effectiveness between probabilistic and deterministic ICERs	Large

Abbreviations: ICER, incremental cost-effectiveness ratio

Leniolisib for APDS in people 12 years and over

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- ❑ Modelling and cost effectiveness
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Key clinical evidence

Leniolisib has been tested in 38 people with APDS across 3 clinical trials

Dose trial and extension trial
Analysis populations

	2201 Part II – pivotal randomised controlled trial (n=31)
Design (duration)	Phase 3, triple-blind, randomised, placebo-controlled study (12 weeks*)
Population	12 to 75 years with a documented APDS genetic P13K delta mutation (body weight ≥45 kg) • nodal and/or extra nodal lymphoproliferation and ≥ 1 measurable nodal lesion on CT/MRI • clinical findings and manifestations compatible with APDS Exclude: surgical or medical conditions, inc HSCT that could affect leniolisib pharmacokinetics
Intervention	Leniolisib 70 mg, twice daily
Comparator	Placebo plus selected symptomatic treatments
Primary outcome**	Immunophenotype normalisation: change from baseline in % of naïve B cells out of total B cells • B-PD analysis set: only participants with less than 48% of naïve B cells at baseline Lymphadenopathy (enlarged lymph nodes): change from baseline in index lymph node size • PD analysis set: excluded participants with zero lesions at baseline.
Key secondary outcomes	• Reductions in size of non-index and index lesions (nodal/lymph node) and spleen • Patient-reported outcomes including SF-36, safety parameters including adverse events
Locations	10 sites, 9 countries, including UK
Used in model?	Yes – also data from extension trial, EAP survey, expert elicitation and ESID registry

* Due to restrictions on immunosuppressant use, duration longer than 12 weeks considered unethical but long enough to show endpoints improvements ** Primary outcomes are surrogate to assess immune dysregulation and deficiency
Note: EAG highlight there are baseline differences between groups – placebo group potentially more severely affected

Abbreviation: HSCT, hematopoietic stem cell transplant; EAP, early access programme; PD, pharmacodynamic; ESID, European Society for Immunodeficiencies

Clinical trial results

Secondary outcomes: immunophenotype and immune dysregulation measures, immune deficiency measures , adverse events and HRQoL

Leniolisib gave a statistically significant decrease in lymphadenopathy and increase in naïve B cells levels after 12 weeks of treatment, which were maintained throughout Study 2201E1

2201 Part II at Day 85	1. Adjusted mean CfB (SE) 2. Mean change (SE)	Comparison of adjusted means			Clinically meaningful response*		
		Difference (SE)	95% CI	p-value	N (%)	Risk difference (CI 95% CI)	p-value
1. Immunophenotype normalisation - change from baseline of percentage of naïve B cell to total B-cells							
Primary efficacy analysis (B-PD analysis set) (n=13)							
Leniolisib (n=8)	37.39 (5.35)	37.30 (5.74)	24.06, 50.54	0.0002	NP	NP	NP
Placebo (n=5)	0.09 (6.66)						
Supportive analysis (PD analysis set) (n=21)							
Leniolisib (n=13)	34.70 (5.66)	27.94 (6.09)	15.02, 40.85	0.0003	12 (100)	1.00 (0.48, 1.00)	<0.001
Placebo (n=8)	6.76 (5.67)				0 (0)		
2. Lymphadenopathy - Change from baseline in log10 transformed SPD of index lesions							
Primary efficacy analysis (PD analysis set: log10 transformed SPD)							
Leniolisib (n=18)	−0.27 (0.04)	−0.25 (0.06)	−0.38, −0.12	0.0006	NP	NP	NP
Placebo (n=8)	−0.02 (0.06)						
Supportive analysis (PD analysis set: sum of square root of the product of diameters)							
Leniolisib (n=19)	−23.68 (4.17)	−21.91 (6.86)	−36.12, −7.69	0.0042	17 (89)	0.64 (0.16, 0.89)	0.002
Placebo (n=8)	−1.78 (6.11)				2 (25)		

*Post hoc responder analysis. Clinically meaningful response after 12 weeks elicited from 24 clinical experts:

- Change of ≥20% in % of naïve B cells / total B cells (normal ranges from 48–84%)
- Median change of ≥20% (in adults) or ≥25% (in adolescents)

Abbreviations: SPD, Sum of the products of two largest perpendicular diameters of lesions; NP, not provided; SE, standard error; CI, confidence interval; CfB, change from baseline; HRQoL, health-related quality of life

Indirect treatment comparison (ITC)

ITC conducted to validate Study 2201 Part II conclusions about leniolisib using a standard care arm more representative of current UK clinical management

Leniolisib arm: Study 2201E1; **Control arm (SoC)**: Eligible people with APDS from ESID registry
Endpoints: Respiratory infections and serum IgM values
Statistical analysis: inverse probability of treatment weighting (IPTW) used to minimise differences at baseline

	Respiratory infections	Serum IgM
Covariates (expert opinion)	Age, baseline IRT use, baseline infection rate	Age, sex, baseline serum IgM levels, APDS mutation status
Remaining imbalances	Receiving IRT, serum IgM, baseline infection rate and APDS type	Baseline infections, follow-up concomitant medication
Results	**Statistically significantly lower rate of respiratory infections with leniolisib compared with SoC** • Estimated annualised infection rates: leniolisib 0.45 (95% CI: 0.3-0.7) and control 1.34 (95% CI: 0.9-2.0) • Rate ratio for annualised respiratory infection rate: 0.34 (95% CI: 0.19, 0.59)	**Leniolisib reduced serum IgM more than SoC** • Median annualised change in IgM: -1.09 g/L (95% CI: -1.78, -0.39, p=0.002) • Treatment effect: -1.09 g/L (95% CI: -1.65, -0.53, p=0.001) per year

EAG: Results show improvements in serum IgM levels and respiratory infection rates consistent with trial
- Eligibility criteria for treatment and control group not matched (no age or weight restriction for control)
- IPTW analyses not always successful in balancing groups for all baseline characteristics

Does the ITC address the Study 2201-part II control arm generalisability issues? Do these results affect the interpretation of the leniolisib treatment effect seen in Study 2201-part II?

Abbreviations: IgM, immunoglobulin; IRT, immunoglobulin replacement therapy; SoC, standard of care; ESID, European Society for Immunodeficiencies

Key issue: Uncertainties in the key clinical trial [1]

Background

- Study 2201 Part II comparator arm: placebo plus a restricted selection of symptomatic treatments
  - Nearly all participants had concomitant medication alongside leniolisib or placebo
- Concomitant treatments included steroids, antimicrobials, IRT and antibiotics
- Previous (unless washout period completed) or concurrent use of some immunosuppressive medication were prohibited (e.g., rituximab, mTOR inhibitors) because may increase infection susceptibility and allow unbiased assessment of efficacy in treating lymphoproliferation

EAG: Excluding treatments used in UK clinical practice raises concerns about generalisability of the comparator

- Baseline imbalances, novelty of surrogate primary endpoints, and a small sample size introduces uncertainties in true magnitude of effect, warranting a cautious interpretation of the results

Company

Comparator arm:

- Acknowledged mTOR inhibitors and rituximab are part of UK current clinical management
- 4/5 clinicians agree would not prescribe some immunosuppressive medications alongside P13K delta inhibitor
  - Trial concomitant medication generally reflective of how leniolisib would be used in practice
- Provided ITC using external control arm from ESID registry – care received better reflects standard care

Baseline imbalances:

- Baseline imbalances may be due to reporting issues across sites and the limited sample size
- English clinicians agreed baseline characteristics were generalisable to individuals seen in routine practice
- Baseline characteristics are comparable with ESID registry (mostly from England)

Abbreviations: ITC, indirect treatment comparison; ESID, European Society for Immunodeficiencies; mTOR, mammalian target of rapamycin

Key issue: Uncertainties in the key clinical trial [2]

EAG comments

Comparator arm:

- EAG clinical advice: immunosuppressive medication, specifically mTOR inhibitors, steroids and rituximab typically form established clinical management for APDS in UK
  - Excluding these treatments for the placebo group is a substantial limitation
  - Placebo group treatment regimen considered less intensive than expected in current clinical practice
- Company's ITC partially address concerns about generalisability

Baseline imbalances:

- Generally comparable, except prior sirolimus treatment more common in placebo (30%) than leniolisib (19%)
- Substantial imbalances: bronchiectasis and gastrointestinal disorder more prevalent in control group
- Agree balancing baseline characteristics in heterogeneous, ultra-rare populations is difficult, but data shows control arm were more severely impacted at baseline compared to leniolisib
  - Potentially bringing uncertainty into observed treatment effect for leniolisib
- Potential cumulative impact of this and comparator arm issues which is less intensive than UK SoC
- Model inputs based on RCT may overestimate leniolisib cost-effectiveness if comparator group differs from the current clinical management arm in the model

Is the comparator arm reflective of UK clinical practice? Is the clinical evidence from Study 2201 Part II appropriate to use in the model and for decision-making?

Abbreviation: RCT, randomised controlled trial; mTOR, mammalian target of rapamycin; SoC, standard of care; ITC, indirect treatment comparison

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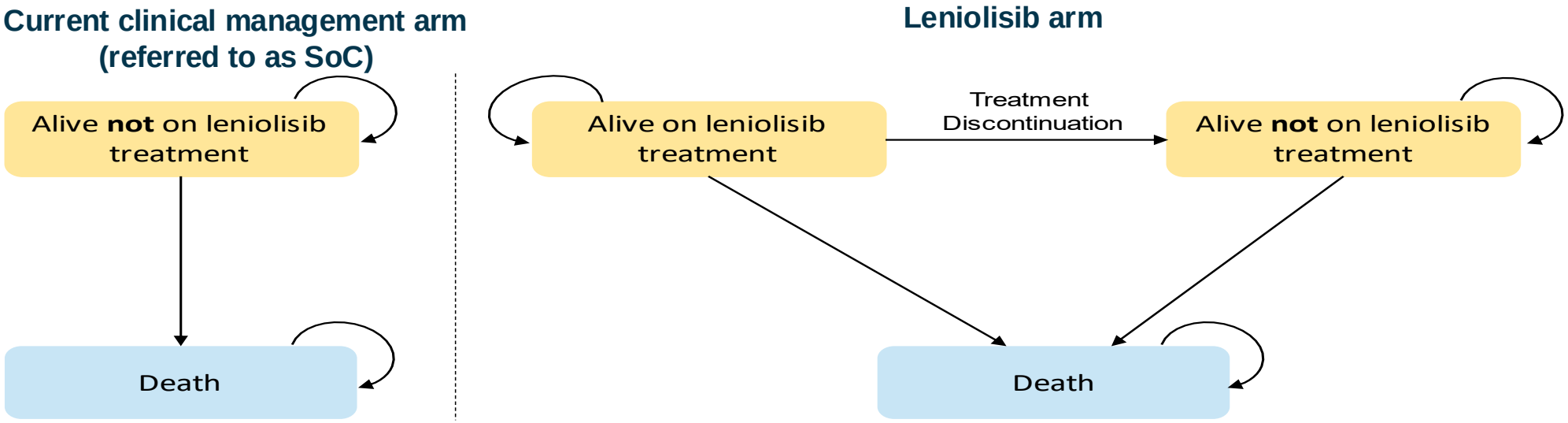
Company's model overview

Company's model decision problem

- Leniolisib benefits modelled via resolved / reduced incidence and severity of manifestations and reduced treatment use
- Company: model structure allows model to track average age-dependent onset of multiple, key manifestations and associated treatments at a cohort level, in line with the progressive nature of APDS
- In each alive health state, manifestation prevalence and treatment utilisation were estimated using a partitioned approach

Model structure



Technology affects costs:	○ High cost of leniolisib ○ Reduces manifestations treatment and monitoring costs ○ If discontinue leniolisib = manifestations increase = treatment use increases
Technology affects QALYs:	○ Reduces manifestations = reduced leniolisib QoL decrement ○ If discontinue leniolisib = manifestations increase = driver of QoL differences
Assumptions with greatest ICER effect:	○ Discount rate: 1.5% (health effects), 3.5% (costs) ○ Utility gain from leniolisib emotional impact ○ No treatment waning ○ QALY gain weight

Abbreviations: SoC, standard of care; QALY, quality-adjusted life years; QoL, quality of life; ICER, incremental cost-effectiveness ratio

Key issue: Lifelong treatment effect [1]

Background

- Company: assume that benefits of leniolisib (whilst on treatment) will be sustained throughout patient's lifetime
- EAG: no evidence that the efficacy of leniolisib will continue beyond 6 years
- Treatment waning explored by varying the discontinuation rate (large impact on ICER)

Company

1. **Treatment effect waning not expected given leniolisib mechanism of action**
   - 6 UK clinicians: agree based on the technology, do not expect treatment response to diminish over time
   - No obvious mechanism for development of leniolisib resistance (unlikely to develop antibodies)
2. **No other mechanism causes APDS so people cannot continue to progress while on treatment**
   - No evidence that it naturally resolves / become less severe long-term
   - Leniolisib normalises P13K delta pathway by reducing its activity without over-inhibiting it → leads to restored immune function which should be maintained for as long as on treatment
3. **No clinical reason effects would be lost except poor adherence or discontinuation**
   - No loss of efficacy/treatment waning reported in clinical trials or EAP, with up to 6 years of data
   - Study 2201: 99% adherence; US leniolisib study: 99% adherence, 2.6 average days off treatment
   - Expect high adherence in long term as symptoms may rapidly return for people who are less adherent
     ↳ Discontinuation suggests lack of efficacy – expect people would return to SoC or improve adherence
   - One way of modelling poor adherence would be an increase in the discontinuation rate
     ↳ Base case: 3.54% annual discontinuation rate (see treatment discontinuation issue)

Abbreviations: ICER, incremental cost-effectiveness ratio; EAP, early access programme; SoC, standard of care

Key issue: Lifelong treatment effect [3]

EAG comments

- EAG's clinical experts: no long-term data to support or refute sustained efficacy over time
  - Uncertain if leniolisib effectiveness will remain constant over the patient's lifetime
  - Obtaining longer term data is the best way to establish if the efficacy of leniolisib will be sustained
- Concerned that high adherence assumed by the company may be an overestimation
- Need to explore treatment waning in model but acknowledge difficulty to include given the available data

Modelled treatment waning:

1. Base case: treatment waning explored through total discontinuation (14%) from treatment
   - Assesses impact of treatment adherence and possibility of discontinuation due to effectiveness waning
   - Approach has a significant limitation of excluding the cost of leniolisib treatment
   - 14% - based on mean discontinuation estimate from company's expert elicitation exercise
2. Alternative method: assume waning does not lead to treatment discontinuation (remain on leniolisib despite decreased efficacy - vary effectiveness across model cycles)
   - Not tested due to time constraints and lack of data on how treatment effect would wane

- Does the committee think the benefits of leniolisib will be sustained over time whilst on treatment?
- If so, how should this be modelled – change in discontinuation rate or varying effectiveness per cycle?

Abbreviations: AE, adverse events; QALY, quality-adjusted life years; SoC, standard of care

Key issue: Treatment discontinuation [1]

Background

- **Company**: assume 3.54% discontinue leniolisib each year; **EAG**: assume 14% discontinue each year
- As the discontinuation rate increases (reduction in leniolisib long-term efficacy), leniolisib becomes more cost-effective (driven by the reduction in drug cost associated with discontinuing leniolisib)

Company

- Base case discontinuation rate based on Study 2201E1 and EAP (n=7) - none stopped from lack of effect
- 5 clinicians estimated the proportion expected to discontinue treatment at any point, for any reason:
  - Mean (SD): 14% (11.40%); median: 10%; individual responses: 30%, 20%, 10%, 10%, 0%
  - Potential reasons: patient choice, not noticing clinical improvement, compliance, had HSCT, AEs
- Uncertain how rate of manifestations and treatment use would change upon leniolisib discontinuation
  - No real-world evidence available
  - Some evidence from Study 2201: 6 people had treatment gap between trials (average 233 days)
    - ↳ During this time, IgM levels increased, and naïve B cells decreased
    - ↳ 1 had 15-month gap - spleen volume increased >200%
    - ↳ After re-starting leniolisib, IgM and naïve B cells improved, and spleen size reduced

Abbreviations: EAP, early access programme; SoC, standard of care; SD, standard deviation; AE, adverse events; HSCT, hematopoietic stem cell transplant; IgM, immunoglobulin

Key issue: Treatment discontinuation [2]

Company continued

Modelling of discontinuation in leniolisib arm

- People who discontinued leniolisib have increased risk of manifestations, treatment use and mortality
- Modelled as constant linear increases for each manifestation/treatment, equivalent to average annual incidence of each manifestation/treatment up to age last patient reported incidence of manifestation / treatment use in ESID registry
  - Assuming risks immediately match SoC arm would ignore time needed for immune system to change and for a period, people would have higher incidence than those who never had leniolisib = overestimate

EAG comments

- Given lack of longer-term data, rate of manifestations/treatment use post-discontinuation seems reasonable
- Would welcome exploration of relationship between discontinuation and development of manifestations

NICE technical team considerations

- At 100% discontinuation from leniolisib arm after 1 year, 2.36 incremental QALYs (3.5% discount rate)
  ↳ Suggests 1 year of treatment provides lifelong benefits (see next slide)

- After discontinuation, how quickly should people revert to SoC manifestations and treatment use?
- Has this return to SoC manifestations and treatment use been modelled accurately?
- What is the most appropriate discontinuation rate to model?

NICE

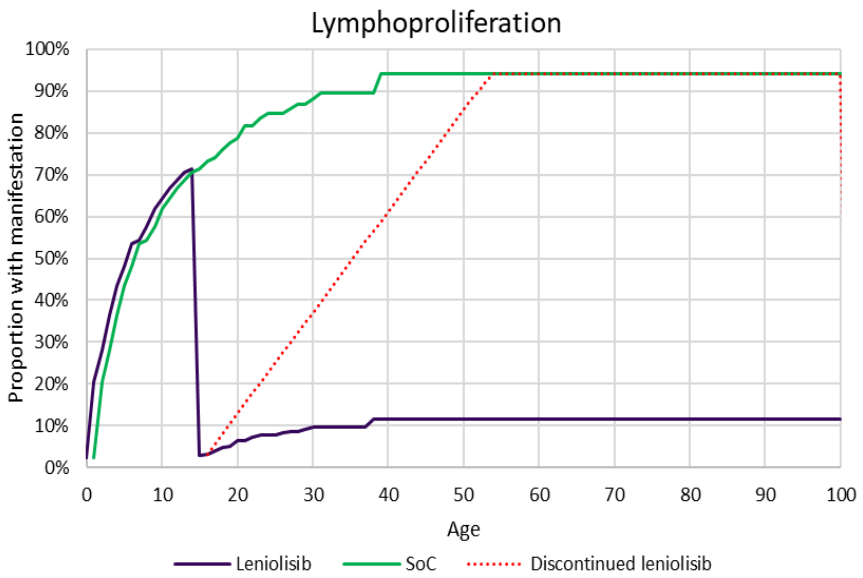
Abbreviations: QALY, quality-adjusted life years; SoC, standard of care; ESID, European Society for Immunodeficiencies

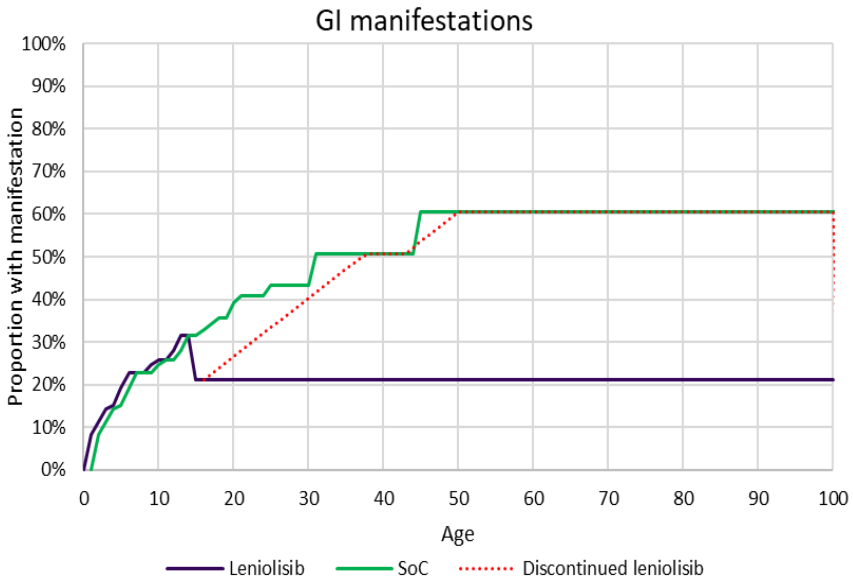
Impact of 3.54% discontinuation

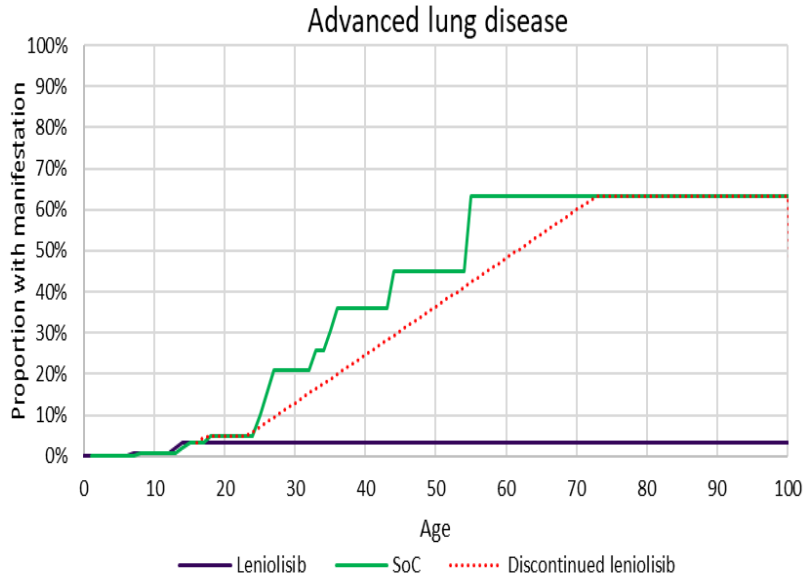
Key issue: Treatment discontinuation [3]

Impact of discontinuation on modelled manifestations (100%)

Undiscounted LYG:
- SoC: [redacted] years
- Leniolisib: [redacted] years







Manifestations (age both groups achieve the maximum cumulative rate of manifestation)	Maximum manifestation rate in each group (A)	Age manifestation rate for "off Leniolisib" group (B)	Age maximum manifestation rate for SoC group (C)	Gap in years between groups (D) = B-C
Lymphoproliferation	93.95%	54	38	16
Gastrointestinal	60.64%	51	44	7
Cytopenias	28.62%	52	40	12
Infections	97.05%	43	43	0
Malignancies	61.77%	61	46	15
Advanced lung disease	63.38%	73	54	19
Hearing loss	25.62%	63	53	10

Abbreviation: SoC, standard of care; LYG, life years gained

Key issue: Utility gain from emotional benefit [1]

Overview of modelled HRQoL

Background

- Company: leniolisib reduces people's emotional burden due to lower expected risk of developing manifestations, reduced mortality, and increased hope due to availability of new treatment
  - Applied additional utility gain (0.1) to capture overall improvement in wellbeing of people treated with leniolisib, including increased vitality and reduced anxiety, and improvements not captured within model
- EAG: insufficient justification regarding quantification of this additional impact on utility

Company

- APDS has broad and substantial emotional impacts including stress, depression, fatigue and constant anxiety about unpredictability and APDS progression, often accompanied by a sense of hopelessness for future
- Study 2201: patients reported improvements e.g., increased energy, improved future outlook and improvements in manifestations → not captured within the model = underestimate leniolisib potential benefit
- Case reports and patient narratives: leniolisib improves some manifestations, but does not fully resolve them
- Previous studies have quantified impact of a positive view, optimism and anxiety on QoL using EQ-5D,
  - Magnitude of these impacts were similar, with a utility gain of between 0.11 – 0.17
  - Anticipate leniolisib QoL benefits will extend beyond these 3 factors (e.g. increased vitality benefit)
- No uncertainty in PSA assumed as utility gain based on differences in utilities from published studies
  - Scenario: 10% SE (utility gain: 0.08 - 0.12) had limited impact = ICER is robust to this assumption

Abbreviation: QoL, quality of life; ICER, incremental cost-effectiveness ratio; APDS, activated phosphoinositide 3-kinase delta syndrome; PSA, probabilistic sensitivity analysis

Key issue: Utility gain from emotional benefit [2]

Utility gain from emotional benefit has a large impact on the ICER

Note: based on company base case assumptions with 3.5% discount rate for costs and health effects

Abbreviation: SoC, standard of care; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; LYG, life years gained

Key issue: Utility gain from emotional benefit [3]

EAG comments

- Understand leniolisib may have positive impacts on patients' emotional state, affecting HRQoL in addition to effect captured by conventional EQ-5D measures
- Concerned about validity of this assumption because:
  1. EQ-5D contains anxiety and depression dimension - may double count if include additional psychological impact
  2. Unsure if 3 studies used to justify assumption were identified using a systematic search and unclear if there is evidence of other relevant studies to inform this assumption
  3. Studies based on different cohorts of patients (different conditions in different countries) - generalisability of results to APDS patients is uncertain
  4. One study is based on unvalidated study-specific questionnaires → biased utility gain estimates
- Evidence used to justify utility gain is highly uncertain and likely to bias cost-effectiveness results
- EAG has removed this assumption from their base-case analysis
- Further evidence on utility impact of reduced emotional burden from leniolisib would help evaluate assumption validity

Should an additional treatment-related utility gain be added to account for the potential emotional benefits of leniolisib?

Abbreviations: HRQoL, health-related quality of life; APDS, activated phosphoinositide 3-kinase delta syndrome

Key issue: Non-reference case discount rate [1]

Background

- Company: 1.5% discount rate applied to health benefits, 3.5% discount rate applied to costs
- NICE 1.5% discount rate criteria:
  1. The technology is for people who would otherwise die or have a very severely impaired life
  2. It is likely to restore them to full or near-full health
  3. The benefits are likely to be sustained over a very long period

Company

Criterion 1: The technology is for people who would otherwise die or have a very severely impaired life

- NICE HST criterion 3 met - "reasonable to conclude that APDS reduces the quality and length of life"

Leniolisib is for people who would otherwise die

- APDS case studies: 25% do not survive to early adulthood and at age 65, there is a 25% survival probability
  - Literature likely underestimates mortality as APDS only recently recognised as condition
- ESID registry: 50% had malignancy or death by age 40, rising to 73% by age 57

Leniolisib is for people who would otherwise have a very severely impaired life

- APDS onset occurs very early in life: median age of 1st manifestation (1 year), 3 manifestations (7 years) and 6 manifestations (33 years) → by adolescence, most have multiple life-limiting manifestations
- Clinical experts EQ-5D vignette study: highest utility value for people with 5 manifestations (0.412) and 8 manifestations (–0.014), suggests clinicians perceive there to be substantial HRQoL burden
- People have intensive treatment regimens with frequent and prolonged hospital visits with invasive treatments
- Current treatments do not target cause, so people still progress and have life-threatening manifestations

Abbreviation: HRQoL, health-related quality of life; APDS, activated phosphoinositide 3-kinase delta syndrome; ESID, European Society for Immunodeficiencies

Key issue: Non-reference case discount rate [2]

Company continued

Criterion 2: It is likely to restore them to full or near-full health

- Leniolisib targets underlying pathophysiology of APDS, leading to improved immune system functioning
- It can resolve manifestations in substantial proportion of people - likely to restore full or near-full health

Improvements in immune dysregulation measures

- Leniolisib resolves / reduces incidence of swollen lymph nodes across body - associated with improved HRQoL
- EAP: leniolisib led to clinically meaningful improvement or remission in 80% of people with cytopenia, 86% with gastrointestinal manifestation and 96% with lymphoproliferation
- Study 2201E1: no signs of rescue medication

Improvement in immune deficiency measures

- Trials and EAP: leniolisib lowers infection rates, prevents bronchiectasis progression, reduces risk of long-term organ damage, improves HRQoL, restores immune system functioning and stops/decreases IRT reliance
- Rao et al., (2024) - 6 people had ≤6 years of leniolisib - helped people return to work and lead more normal life

Criterion 3: The benefits are likely to be sustained over a very long period

- Leniolisib directly addresses root cause of APDS = long-term benefits in both immune dysregulation and immune deficiency leads to reduced use / no supportive medications and HRQoL improvements
- Expect treatment to begin early (age 12) - 1.5% avoids large reduction in value of long-term health benefits
- Leniolisib mechanism of action - not biologically plausible to expect treatment effect waning
- Clinical trial and EAP: long-term leniolisib efficacy supported by 200+ patient years of exposure with no waning

Abbreviation: EAP, early access programme; APDS, activated phosphoinositide 3-kinase delta syndrome; HRQoL, health-related quality of life; IRT, Immunoglobulin replacement therapy

Key issue: Non-reference case discount rate [3]

Modelled manifestation and treatment use

EAG comments

- Deviation from NICE reference case – insufficient justification and criteria not sufficiently met
- Agree effectiveness evidence suggests leniolisib substantially decreases rate of APDS manifestations, alleviating patient's symptom burden, which may lead to significant improvements in QoL and life expectancy
- Uncertainty in effectiveness and duration of leniolisib:
  - Leniolisib does not appear to eliminate manifestations in all patients
  - Due to lack of long-term data and mean age of participants starting treatment (15 years old in model), remains unclear whether participants would regain full health or near full health
  - Lack of longer-term data = uncertain whether benefits will be sustained over a very long period
- Longer-term follow up data would provide evidence needed to assess whether criteria are fully met
- Recommend 3.5% discount rate is applied to both costs and effects in the base-case analysis

Other considerations

- NICE HST criteria 3: uncertainty about extent that 'APDS reduces the quality and length of life' would apply to all people with ADPS because of condition heterogeneity and small amounts of available evidence
- NICE manual (section 4.5.2): "The committee may consider analyses using a non-reference-case discount rate of 1.5% per year **for both costs and health effects"** – cannot apply differential discount rates
- Setmelanotide for treating obesity (HST21): company only discounted health effects at 1.5% - committee concluded differential discounting not appropriate

Have all 3 criteria been met? If so, should a 1.5% discount rate be applied to health effects and costs?

Abbreviations: QoL, quality of life; APDS, activated phosphoinositide 3-kinase delta syndrome

Key issue: Modelling uncertainty

Background

- Company: assumed SE of 10% of the mean for parameters where uncertainty information was not available
- EAG: 10% not justified - used for most key model inputs for utility, costs and HR for manifestation rates
- There is a large difference in deterministic and probabilistic ICERs, but the SE assumed has small impact
  - Results carry high degree of uncertainty surrounding costs and effects - suggests more research needed

Company

- Review of NICE STAs (2013-2014) found 68% had ≥1 parameter where variation (SE) assumed and not informed by data → SE assumed to be 10-30% of mean, with 20% being most common
- Consistency of PSA and deterministic results (using 10% SE) indicates absence of non-linearities in model

EAG comments

- Acknowledge company's 10% SE assumption is within 10-30% range from the review, but doesn't justify:
  1. Choice of 10% (lower bound of range) implies high level of precision and certainty about estimate
     - Does not seem appropriate given estimates were not based on directly relevant empirical evidence
  2. Assumption applied to large proportion of parameters
  3. Company did not report if they checked that 10% SE adequately covers uncertainty in expert estimates
- Company 20% SE scenario analysis shows cost-effectiveness probability dropped by 5% = moderate impact
- Prefer 20% SE for parameters where there is no uncertainty information - more conservative approach
- In future, further information about key input parameters uncertainty levels needs to be obtained

Is uncertainty appropriately captured within the PSA? What is the most appropriate SE to use in the PSA where uncertainty information is unavailable?

Abbreviations: PSA, probabilistic sensitivity analysis; SE, standard error, HR, hazard ratios; ICER, incremental cost-effectiveness ratio

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must consider the QALY gain magnitude and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply a QALY weight, there must be compelling evidence that treatment offers significant QALY gains

Inc undiscounted QALY gains	QALY weight	ICER threshold applied to discounted ICER
Less than or equal to 10	1	£100,000 / QALY
11 to 29	Between 1 to 3 (equal increments)	£100,000 to £300,000 / QALY (equal increments)
Greater than or equal to 30	3	£300,000 / QALY gained

Assuming 3.5% discount rate	Inc QALYs - undiscounted
Company base case (deterministic)	14.78
Company base case (probabilistic)	16.20
EAG base case (deterministic)	5.86
EAG base case (probabilistic)	7.60

Can QALY weighting be applied to company and EAG base cases?

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Cost-effectiveness assumptions and results

One way sensitivity analysis

Assumption	Company base case	EAG base case
Discount rate	1.5% for health effects, 3.5% for costs	3.5% for cost and health effects
Treatment discontinuation rate	3.54%	14%
Leniolisib emotional utility gain	Included	Excluded
PSA standard error	10%	20%

Company base case scenario (3.5% discount rate)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case (deterministic)	See part 2	See part 2	Over £100,000
Company base case (probabilistic)	↓	↑	Over £100,000
20% SE for inputs without uncertainty (vs probabilistic)	↓	↓	Over £100,000
Treatment discontinuation rate = 14%	↓	↓	Over £100,000
Treatment discontinuation rate = 30%	↓	↓	Under £100,000
Exclude emotional utility gain	↔	↓	Over £100,000
1.5% discount rate costs and benefits	↑	↑	Over £100,000
EAG base case (deterministic)	↓	↓	Over £100,000
EAG base case (probabilistic)	↓	↓	Over £100,000

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SE, standard error

Leniolisib for APDS in people 12 years and over

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Factors affecting the guidance

In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

QALY, quality adjusted life year; QoL, quality of life

Uncaptured benefits

Carer perspectives

Company: several leniolisib benefits not captured in the QALY so benefit may be underestimated

Clinical benefits

- Leniolisib may result in clinical benefits in non-immune cells → improvements in these manifestations e.g., allergies and asthma are not modelled because based on lack of available evidence = may underestimate leniolisib benefit

Benefits to individuals' work and education

- Leniolisib may improve productivity and increase working hours at work/school, hence wider societal benefit:
  - Study 2201: people reported an increase in hours worked / in class, maintained in Study 2201E1
  - Study 2201 Part II: people reported improvements in impairment experienced whilst working due to health

Burden to the NHS benefits

- Leniolisib reduces need and burden of IRT on patients and NHS → supports supply chain easing, and reduced risk of transferring new infections and disease (IRT burden continues to be a significant discussion topic in UK)
- Leniolisib reduces the need for antibiotics, decreasing the incidence of individuals with antimicrobial-resistant infections, alongside associated high costs and burden

Caregiver HRQoL benefits

- Many people with APDS need physical and emotional support from caregivers who may be impacted by stress and need take time off from work to take care of or home-school their dependent
- Leniolisib improves manifestations associated with APDS which can positively impact caregiver HRQoL

UK Rare Disease Strategy

- In line with UK Rare Disease Strategy, leniolisib would provide an effective treatment option, promoting equitable access across UK licensed APDS population

Abbreviations: IRT, immunoglobin replacement therapy; QALY, quality-adjusted life years; APDS, activated phosphoinositide 3-kinase delta syndrome; HRQoL, health-related quality of life

Leniolisib for APDS in people 12 years and over

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Issue	ICER impact
Uncertainties in the key clinical trial ○ Clinical trial comparator arm excluded treatments used in current clinical management so may not be generalisable to UK practice ○ Baseline imbalances, novel surrogate primary endpoints, and small sample size	Unknown
Lifelong treatment effect assumed ○ Company assume that there is no waning of leniolisib effect for the duration of treatment	Large
Treatment discontinuation ○ Company model a slow loss of treatment effect after stopping leniolisib treatment	Large
Utility gain from emotional benefit ○ Company assume leniolisib reduces APDS emotional burden by lowering expected risk of developing manifestations, reducing mortality, and increasing hope due to new treatment	Large
1.5% non-reference case discount rate ○ Company applied a 1.5% discount rate to health effects and 3.5% discount rate to costs	Large
Model uncertainty – probabilistic sensitivity analysis ○ Company assume a standard error of 10% of mean for inputs with no uncertainty information ○ Large difference in cost-effectiveness between probabilistic and deterministic ICERs	Large

NICE

Abbreviations: ICER, incremental cost-effectiveness ratio

Leniolisib for APDS in people 12 years and over

Supplementary appendix

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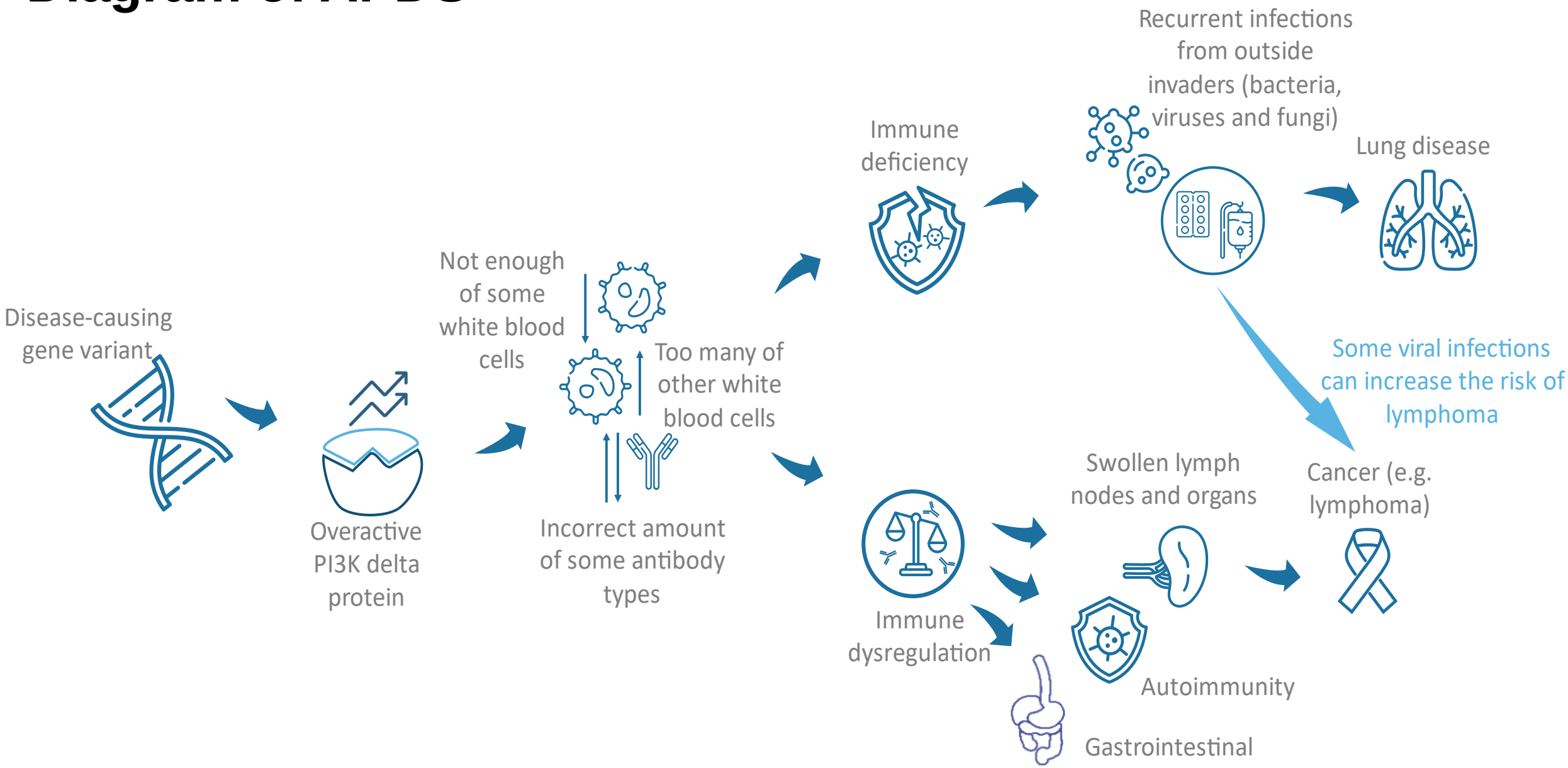
Diagram of APDS

Background on APDS



Abbreviation: P13K, phosphoinositide 3-kinase delt

Immunodeficiency UK with NICE survey summary statistics

Disease and treatment burden

- 14/14 taking medication - 2 are taking 6 medications, 2 taking 4-5 medications
- 13 people over 12 months: 320+ outpatient appointments, 67 inpatient visits, 229 days in hospital
- Over 12 months, average 24.6 outpatient visits, 17.6 days in hospital
- 3/11 need help with personal care e.g., washing, going to toilet, cooking, mobility and administering medication

Impacts of APDS

- Most people reported time to diagnosis of more than 3 years
- 12/14 reported significant time out of education from several weeks to years
- 10/14 had mental health impact due to feelings of depression, burden of care, confusion, frustration, moderate and extreme anxiety, isolation and loneliness
- 12/12 reported pain and discomfort in relation to APDS – 1 reported extreme pain
- 5 reported an impact on mobility
- 4 reported APDS had an impact on ability to work

Leniolisib

- 6/14 had been treated with leniolisib
- 5/6 reported benefits of leniolisib
- 8/8 would recommend leniolisib
- 3/6 reported drawbacks of leniolisib

Quality of life

- 4/13 were satisfied with their quality of life
- 3/13 have an extreme amount of tiredness
- 11/13 have extreme worries about infections
- 6/13 have extreme health worries
- 7/8 felt that APDS highly affected their family

Abbreviations: APDS, activated phosphoinositide 3 kinase delta syndrome

Natural history studies and expert elicitation

Key clinical trial

Natural history studies

- European Society for Immunodeficiencies (ESID) registry - prospective, observational, international registry of people of all ages with primary immunodeficiencies (PIDs) and the UKPID registry is a major contributor
- Includes cohort with a genetic confirmation of APDS, and is largest registry for people with PIDs worldwide
- Conducted various ESID analyses to investigate APDS characteristics and supplement natural history and clinical care pathway literature

Expert Consultancy project (ECP)

- 3 exercises to address various areas of uncertainty within APDS evidence base and validate key assumptions:
  1. Exercise 1: modified structured expert elicitation
     - Aim of generating estimates of long-term impact of leniolisib on APDS manifestations and mortality
     - Elicit upper/lower estimates of APDS survival and manifestations occurrence in SoC and leniolisib
     - Calculated HRs estimating likelihood of manifestations and survival after leniolisib vs SoC
  2. Exercise 2: EQ-5D-5L survey (vignette study)
  3. Exercises 3 and 4: qualitative and quantitative surveys to generate/validate submission & model assumptions
- 10 clinical experts with APDS expertise from UK, Europe and Canada. English experts took part in all exercises
  - Exercise 1: 5 people with experience treatment people with leniolisib (UK, Europe, Canda)
  - Exercise 3 and 4: 5 people, England and Italy
- Had chance in exercise 1, 3, 4 to say if particularly unsure, or lacked relevant experience / expertise to answer
  - Sensitivity analyses conducted where these responses were excluded from combined results
- Had follow-up calls after each exercise to enable validation of results, and clarification of certain responses

Abbreviation: APDS, activated phosphoinositide 3-kinase delta syndrome; SoC, standard of care

Surrogate co-primary outcomes

Key clinical trial

Company say the co-primary endpoints measure hallmark manifestations of APDS - immunophenotype normalisation and reduction in lymphoproliferation

Company:

- APDS treatment aims to normalise immune system and reduce lymphoproliferation
- Large variability in clinical outcomes so to use them as primary outcomes would need large sample size
- APDS experts, EMA and FDA reached consensus that naïve B cells and lymphadenopathy are clinically meaningful endpoints that influence clinician decision-making in short-term and translate into long-term benefit

Immunophenotype changes (clinical trial results)

- 74% (leniolisib) and 14% (placebo) with abnormally low baseline naïve B cells had normal levels by 3 months
- Improvements maintained: naïve B cell increase from 66% to 74% from Study 2201 Part II to Study 2201E1
- Study 2201E1 post-hoc analysis: increased naïve B cells significantly predicts reduced infection rates
- 89% of PtGA treatment effect explained by naïve B cells = immune system normalisation patient-relevant benefit

Lymphoproliferation (clinical trial results)

- Statistically significant reduction in size of lymphadenopathy: Study 2201 Part II (-43%) and 2201E1 (-49.5%)
- Post-hoc results indicate association between change in index lesion SPD and patient global assessment
- Study 2201 Part II: large reductions in lymphadenopathy at all sites - indicates decrease in disease activity

EAG comments:

- Uncertain about validity of surrogate endpoints in reliably predicting long-term benefits that reflect patient benefit
- Despite some biological plausibility and data supporting measure of naïve B-cells, evidence of consistent association remains unclear

NICE

Abbreviation: APDS, activated phosphoinositide 3-kinase delta syndrome; EMA, European medicines agency; FDA, food and drug administration; PtGA, patient global assessment; SPD, Sum of the products of two largest perpendicular diameters of lesions

Additional clinical trials

Key clinical trial

	2201 Part I - dose-finding study	2201 Part EI – extension of 2202 Part II
Design, duration	Phase 2, open-label, non-randomised, within-participant, dose escalation study (n=6), 12 weeks	Single-arm, non-randomised, open-label extension study (n=37), 6 years, 3 months
Population	12 to 75 years with documented APDS genetic P13K delta mutation (body weight ≥45 kg) • nodal and/or extra nodal lymphoproliferation • ≥ 1 measurable nodal lesion on CT/MRI • clinical findings and manifestations compatible with APDS Exclude: surgical or medical conditions, including HSCT that could affect leniolisib pharmacokinetics	12-75 years documented APDS genetic P13K delta mutation (body weight ≥45 kg) Exclude: surgical or medical conditions, including HSCT, that may alter leniolisib pharmacokinetics
Intervention	3 increasing leniolisib doses (10 mg, 30 mg, 70 mg)	Leniolisib 70 mg twice daily
Primary outcome	• Safety parameters including adverse events • Dose concentration • Percentage of Inhibition of Unstimulated and Stimulated pAkt Levels in B Cells	Safety parameters including adverse events
Key secondary outcomes	Patient-reported outcomes including SF-36	• Frequencies of infections and other disease complications • Patient-reported outcomes including SF-36
Locations	10 sites, 9 countries, inc UK (none from England)	8 sites, 7 countries, not UK
Modelled?	No	Yes

Abbreviations: HSCT, hematopoietic stem cell transplant; pAkt, phosphorylated-Serine473-AKT

Early access programme (EAP) survey

Key clinical trial

Company

- Global EAP provides people who were unable to enter clinical trial opportunity to be treated with leniolisib
  - 21/30 physicians completed questionnaires for 30/40 (75%) individuals on leniolisib EAP
  - Most from Europe and Russia, findings generalisable to UK clinical practice
  - Physician survey done to capture additional data on leniolisib clinical benefit across clinically relevant domains
  - Cytopenia, lymphoproliferation, infections, chronic fatigue, gastrointestinal and pulmonary manifestations
- Duration of leniolisib: unlikely all individuals entering with overt manifestations would improve at a specific timepoint only after having leniolisib treatment, so benefit may be underestimated
  - 0-6 months (n=8); 6-12 months: (n=8); 12–24 months: (4=8); >24 months: (n=10)

Results

- Infections and other APDS hospitalisations were decreased after leniolisib (-47% and -50% respectively)
- Non-infectious APDS complications:
  - Clinically meaningful improvement in most domains evaluated as relevant to patients - ranged from 53% (pulmonary) to 88% (lymphadenopathy) - some include complete remission of signs and symptoms
  - Gastrointestinal manifestations: 84% domains improved in meaningful way, 44% going into remission
  - No reported cases of worsening of any manifestations or domains evaluated in the questionnaire
- New disease manifestations - 4 new disease manifestations, associated with natural course of disease
- Immunophenotyping - 53% had trend towards normalisation across 77 domains. Others either missing or stable
- 3/28 had lymphoma pre-leniolisib – 0 have since recurred, 1 new case
- Benefit/risk assessment - 29/30 derived clinical benefit that warrants continued treatment and was well tolerated

Abbreviations: IRT, Immunoglobulin replacement therapy; APDS, activated phosphoinositide 3-kinase delta syndrome; mTOR, mammalian target of rapamycin

Analysis populations

Population	Study 2201		Study 2201E1
	Part I	Part II	
Safety	All participants who received any study drug.		
	N=6 (100.0%)	N=31 (96.9%)*	N=37 (100.0%)
Pharmacokinetic (PK)	All participants with ≥1 available valid PK concentration measurement, who received any study drug and had no protocol deviations with relevant impact on PK data.		
	N=6 (100.0%)	N=19 (90.5%)	N=37 (100.0%)
Pharmacodynamic (PD) **	All participants with any available PD data who received any study drug and had no protocol deviations with relevant impact on PD data.		
	N=6 (100.0%)	N=27 (84.4%)	N=37 (100.0%)
B-PD data set***	PD data - only participants with <48% naïve B cells at baseline were included		
	-	N=13 (40.63%)	-

*N=32, one failed screening

** Used for analysis of primary endpoint change from baseline in size of index lymph node. Patients with 0 nodes at baseline excluded from primary analysis

*** Used for analysis of primary endpoint change in baseline in the % of naïve B cells out of total B cells

EAG: B-PD data analyses a reduced sample and is underpowered, leading to uncertainties in magnitude of effect

- Supportive analysis using full PD data set is provided and demonstrates a similar trend
- To address possibility of multiplicity both primary endpoints need to be statistically significant to draw inferences

Key clinical trial: baseline characteristics

- Company: 5 clinicians in the Expert Consultancy agreed that baseline characteristics in Study 2201 Part II were generalisable to individuals they see in routine clinical practice
- EAG: agree trial results are likely generalisable to APDS patients seen in England

Baseline characteristics		Part I (N=6)	Part II (N=31)			Study 2201E1 (N=37)
			Placebo (n=10)	Leniolisib 70 mg bid (n=21)	Total population (N=31)	
Total participants that completed the study – n		6	10	21	31	37 enrolled (ongoing)
Age (years) – mean (SD)		22.2 (5.64)	26.7 (13.43)	22.2 (10.00)	23.7 (11.19)	22.7 (9.96)
Participants under 18 – n (%)		2 (33.3)	4 (40.0)	8 (38.1)	12 (38.7)	NR
Sex – n (%)	Male	4 (66.7)	4 (40.0)	11 (52.4)	15 (48.4)	21 (56.8)
	Female	2 (33.3)	6 (60.0)	10 (47.6)	16 (51.6)	16 (43.2)
Race – n (%)	White	6 (100.0)	7 (70.0)	18 (85.7)	25 (80.6)	31 (83.8)
	Asian		1 (10.0)	1 (4.8)	2 (6.5)	2 (5.4)
	Black		1 (10.0)	1 (4.8)	2 (6.5)	2 (5.4)
	Other		1 (10.0)	1 (4.8)	2 (6.5)	2 (5.4)
Ethnicity n(%)	Hispanic/Latino	1 (16.7)	1 (10.0)	0	1 (3.2)	3 (8.1)
	Not Hispanic or Latino	3 (50.0)	7 (70.0)	14 (66.7)	21 (67.7)	22 (59.5)
	NR	2 (33.3)	2 (20.0)	7 (33.3)	9 (29.0)	12 (32.4)
Weight (kg) – mean (SD)		63.92 (7.63)	68.55 (11.66)	66.14 (15.55)	66.92 (14.26)	65.88 (12.28)
Height (cm) – mean (SD)		170.63 (9.68)	166.19 (8.15)	163.15 (8.25)	164.13 (8.21)	165.27 (8.90)
BMI (kg/m^2) – mean (SD)		22.10 (3.46)	24.89 (4.35)	24.76 (5.12)	24.80 (4.81)	24.154 (4.37)

Abbreviation: APDS, activated phosphoinositide 3-kinase delta syndrome; SD, standard deviation

Clinical trial results: Study 2201E1

Leniolisib treatment resulted in a clinically meaningful response in lymphadenopathy and increase in levels of naïve B cells after 6 months

		Leniolisib (N=37)
Responder analysis of all participants with an enlarged lymph node at baseline with ≥30% (adults) or ≥45% (adolescents) reduction from Baseline in index lesion SPD		
Day 168/252	Number of participants contributing to the analysis	30
	Number of responders	24
	%	80.0
Responder analysis of all participants with low naïve B cells at baseline with ≥25% increase from Baseline in index lesion SPD		
Day 168/252	Number of participants contributing to the analysis	6
	Number of responders	5
	%	83

Abbreviations: SPD, sum product of diameters

Primary outcomes

Clinical trial results: secondary outcomes [1]

Outcome(s) and associated manifestation(s)	Clinical trial finding and real-world evidence
Immunophenotype measures	• Normalisation of B and T cell development and maturation process, immunoglobulin levels and chemokine and cytokine levels were observed across Study 2201 and Study 2201E1
Immune dysregulation measures	
Lymphoproliferation and splenomegaly	• Post-hoc responder analysis: reduction in index lesion associated with improved physical component on SF-36 and PtGA • Statistically significant reduction in both spleen volume and size in Study 2201 Part II ○ 73% clinically meaningful reduction from leniolisib and 0% from placebo

Cytopenias (autoimmune manifestations)	• 82% of cytopenias improved in leniolisib arm vs 60% placebo arm (Study 2201 Part II)
	  ○ 83% had clinically meaningful response vs 50% in placebo arm
	• Low incidence of cytopenia adverse events were reported in Study 2201E1
	  ○ 78% had clinically meaningful response

Gastrointestinal manifestations	• Leniolisib treatment led to improvements in 2/3 participants who had gastrointestinal manifestations pre-Study 2201 Part II. Both remain symptom-free and have discontinued other treatments for their gastrointestinal manifestations

Abbreviations: PtGA, patient global assessment

Clinical trial results: secondary outcomes [2]

Primary outcomes

Immune deficiency measures	Clinical trial finding and real-world evidence
Rate of infections	• Significant decrease (25%) in annualised infections rates with each extra year of leniolisib • Sustained reductions in IRT use and some individuals achieving IRT freedom • No increase in antibiotic usage, but also no significant reduction throughout Study 2201E1 • No new incidences of deafness reported during Study 2201 Part II or Study 2201E1
Lung disease	• No new bronchiectasis cases in leniolisib arm for Study 2201 part II or Study 2201E1 • 3 got bronchiectasis pre-Study 2201 Part I – none progressed with 6 years of leniolisib
Fatigue	Narratives and RWE indicate leniolisib leads to improved fatigue/ energy - 1/3rd explicitly attributed improvements to leniolisib, 70% describe improvements vs 44% with placebo
Malignancy and mortality	• No reports of clinically significant, new malignancies associated with leniolisib in 3 trials • Short trial duration and small sample – few mortality events expected in Study 2201 Part II
Disease severity and HRQoL	SF-36: baseline role-physical, general health, social functioning and role-emotional below average ○ Study 2201 Part I, II, E1: numerical increase in all SF-36 scales for leniolisib and maintained ○ 12 weeks: no meaningful CfB in all scales and no significant difference between groups ○ General health and role-emotional increased, but still below average for general population ○ Clinically meaningful long-term changes in general health and physical summary PtGA: 2201 Part II clinically meaningful CfB, but not statistically significant difference between groups • Study 2201E1: numerical improvements in PtGA scores for leniolisib group maintained Narrative / qualitative evidence: 100% had positive impact with leniolisib - 86.1% improvement in ≥1 manifestation or HRQoL

Abbreviations: HRQoL, health-related quality of life; CfB, change from baseline; IRT, immunoglobulin replacement therapy; RWE, real world evidence; PtGA, patient global assessment

Clinical trial results: HRQoL

Primary outcomes

SF-36 Scale	Baseline	Week 12 (n=31)	Week 52 (n=28)	Week 130 (n=19)	Week 156 (n=14)	Week 208 (n=10)	Within-Patient Meaningful Change Threshold for SF-36
	Mean (SD)	Mean CfB (SD)	Mean CfB (SD)	Mean CfB (SD)	Mean CfB (SD)	Mean CfB (SD)	
Component Summary Measures							
Physical component summary	46.57 (7.39)	**4.84 (5.81)**	**5.49 (7.28)**	3.17 (6.95)	NR	NR	3.4
Mental component summary	47.87 (8.09)	3.00 (8.89)	2.76 (8.86)	0.54 (7.80)	NR	NR	4.6
Scales							
Physical functioning	48.23 (7.36)	3.75 (5.11)	3.61 (5.89)	2.32 (6.20)	-0.14 (10.28)	**5.36 (4.95)**	4.3
Role-physical	45.57 (8.14)	**4.27 (6.41)**	**4.33 (7.58)**	2.84 (8.98)	**3.69 (8.24)**	2.69 (6.62)	3.4
Bodily pain	50.70 (9.19)	3.14 (8.67)	2.07 (9.01)	3.14 (8.16)	2.65 (5.73)	1.94 (4.82)	6.2
General health	38.54 (9.33)	**8.12 (9.31)**	**7.23 (10.12)**	**10.36 (10.03)**	**11.04 (8.65)**	**9.79 (5.46)**	7.2
Vitality	50.01 (10.37)	4.03 (10.10)	4.99 (10.67)	3.91 (12.25)	3.18 (8.03)	**10.1 (7.16)**	6.2
Social functioning	46.83 (9.54)	3.07 (8.65)	3.58 (8.39)	1.58 (12.06)	0.36 (7.21)	-5.01 (7.92)	6.9
Role-emotional	45.72 (8.43)	3.15 (7.86)	3.11 (7.24)	0.73 (10.16)	-1.49 (9.13)	0.70 (5.16)	4.5
Mental health	48.59 (8.10)	3.46 (9.02)	2.15 (8.78)	3.86 (9.65)	4.11 (5.96)	5.76 (6.24)	6.2

Bold = mean CfB exceeded within-participant meaningful change thresholds
Scales are scored from 0–100, with higher scores indicating better health. <47 at baseline is below average

PtGA

Study 2201 Part II	Mean CfB (SD)	Comparison of leniolisib to placebo	
		Adjusted mean difference (95% CI)	p-value
Leniolisib (n=19)	13.05 (20.71)	9.25 (−5.65 to 24.14)	0.2113
Placebo (n=8)	−2.25 (28.95)		

Study 2201E1	Week 12		Week 208	
	n	Mean CfB (SD)	n	Mean CfB (SD)
Leniolisib	37	-14.66 (21.42)	10	–25.63 (26.62)

EAG:

- SF-36 findings were limited and did not show long-term improvement in HRQoL, with exception of general health scale
- PtGA score findings and participant narratives were more favourable.
- Part I participants said fatigue was important - more robust measure of fatigue would have provided better patient-relevant data

NICE

Abbreviations: bid: Bis In Die (twice daily); CfB: change from baseline; CI: confidence interval; PD: pharmacodynamics; SE: standard error: SPD: sum of product diameters

Clinical trial results: Adverse events

Adverse events nE, nS, (%)	Study 2201 Part I			Study 2201 Part II		Study 2201E1			Total Leniolisib N=38
	Leniolisib 10 mg N=6	Leniolisib 30 mg N=6	Leniolisib 70 mg N=6	Leniolisib N=21	Placebo N=10	Previous Leniolisib N=26	Previous Placebo N=9	Total N=37	
Participants with AEs	4, 2 (33)	3, 2 (33)	11, 4 (67)	92, 18 (86)	46, 9 (90)	286, 24 (92)	112, 8 (89)	418, 34(92)	528, 36(95)
Categories of AEs									
Grade 1	1,1 (17)	2, 1 (17)	9, 3 (5)	65, 15 (71)	27, 8 (80)	182, 24 (92)	27, 6 (67)	228, 32(87)	305, 33(87)
Rates per participant-year: Grade 1	2.2	4.3	18.1	12.7	10.5	2.1	1.2	2.0	2.4
Grade 2	2, 0 (0)	1, 1 (17)	2, 1 (17)	19, 9 (43)	13, 5 (50)	63, 16 (62)	40, 7 (78)	104, 24 (65)	128, 28 (74)
Grade 3	1, 1 (17)	0, 0 (0)	0, 0 (0)	3, 2 (10)	4, 3 (30)	16, 6 (23)	29, 4 (44)	45, 10 (27)	49, 11 (29)
Grade 4	0, 0 (0)	0, 0 (0)	0, 0 (0)	3, 2 (10)	1, 1 (10)	1, 1 (4)	0, 0 (0)	1, 1 (3)	4, 3 (8)
Grade 5	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	1, 1 (10)	1, 1 (4)	0, 0 (0)	1, 1 (3)	1, 1 (3)

Abbreviations: AE, adverse events, nE, number of events, nS, number of people with at least 1 AE in category

Prohibited immunosuppressive co-medications

Examples of prohibited immunosuppressive co-medications in tudy 2202 part II	Time frame within which co-medication was not permitted before first dose
• Belimumab • Cyclophosphamide	• 6 months
• B cell depleting medication (e.g., rituximab)	• 6 months • If previously received, absolute B lymphocyte counts in the blood must have regained normal values
• Cyclosporine A • Mycophenolate • 6-mercaptopurine • Azathioprine • Methotrexate	• 3 months
• mTOR inhibitors (e.g. sirolimus, everolimus) • Non-selective P13K inhibitors • Selective P13K delta inhibitors	• 6 weeks • Short-term use for up to 5 days allowed but only up to 1 month prior to study enrolment
• Glucocorticoids above 10 or 25 mg prednisone or equivalent per day	• 2 weeks
Other immunosuppressive medications where the effects were expected to persist at start of dosing of the study medication were also prohibited	

Abbreviations: mTOR, mammalian target of rapamycin

Company model decision problem [1]

Model overview

EAG considers the company's deviations from reference case have a large impact on cost-effectiveness results

Input	Assumption and evidence source	EAG comment	ICER impact
Population	Adults and adolescents with APDS 12 years of age or older • Model starting age: 15 years • Based on average age of people in level 1 dataset of ESID registry	• Summary ESID information submitted states mean age at registry is 17.7 • Could not verify appropriateness of starting age assumption	Small
Treatments	Leniolisib versus current clinical management (referred to as SoC)		-
Perspective	NHS and Personal Social Services (PSS) perspective	No PSS associated resources included • Concern - manifestations can severely affect patient's daily activities • People may need extra support that could be provided by PSS - may increase APDS associated costs	Unknown
Time horizon	Lifetime horizon (85 years) – leniolisib expected to be taken lifelong after start		-
Cycle length	Annual cycles (with a half-cycle correction)		-
Discount rate	1.5% (health effects), 3.5% (costs)	See 1.5% discount rate	Large
Treatment effect waning	Not included	See treatment effect and treatment discontinuation	Large

Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care; APDS, activated phosphoinositide 3-kinase delta syndrome

Company model decision problem [2]

Model overview

Input	Assumption and evidence source	EAG comment	ICER impact
Utilities (see HRQoL overview)	• Baseline utility: clinician EQ-5D vignette study • Manifestation / treatment use utilities: from proxy conditions or clinician EQ-5D • Leniolisib emotional benefit (issue 4): 0.1 • 50% reduced disutility for people with less severe manifestations from leniolisib	Utilities from proxy conditions may not: • Provide inaccurate estimates of APDS HRQoL impact and complicate utility calculation • use EQ-5D based utilities with UK value set • be representative of UK population	Large
Adverse events	Not modelled but treatment-related disutilities for SoC options included • Trial AE/TEAEs similar in leniolisib and placebo groups	• Placebo group not reflective of UK SoC – efficacy outcomes may differ • Large uncertainty about differences in AE incidence between arms	Unknown
Costs and resource use	• Costs: NHS reference costs, BNF, eMIT and Expert Consultancy • Resource use: clinician elicited estimates • 50% cost reduction for people with less severe manifestations from leniolisib	• Some concerns - most resource use estimates from expert elicitation • Large variation in estimates = true healthcare resource impact uncertain	Unknown

Abbreviation: APDS, activated phosphoinositide 3-kinase delta syndrome; SoC, standard of care; HRQoL, health-related quality of life; AE, adverse events; TEAE, Treatment emergent adverse events

Model overview

Company model decision problem [3]

Input	Clinical parameters
Current clinical management	
Manifestations and treatment use	Age-specific incidence/prevalence of manifestations and age-specific proportions having different treatments based on ESID registry and Study 2201 Part II - validated by expert
Overall survival	Weibull curve fitted to KM data from patient-level data from SLR – validated by clinicians
Impact of leniolisib	
Manifestations and treatment use	Impact of leniolisib on treatment use and incidence and proportions of severity reduction and resolution of manifestations based on 1) Study 2201 Part II / E1, 2) EAP survey or 3) 5 clinicians **EAG:** Concerned estimates from 5 clinicians subject to high level of uncertainty • Sometimes clinical opinions used when higher quality of evidence available - inconsistent use of evidence across groups with different data quality
Overall survival	Leniolisib survival impact elicited from 4 clinicians (mortality not assessed in trial) - HR [redacted] • Scenario: leniolisib survival impact modelled using manifestation-specific morality risk **EAG concerns:** • Estimates subject to high levels of uncertainty – fewer experts than recommended for elicitation and experts may have limited experience treating APDS and using leniolisib • Expert opinion used when real world data is available (but more conservative HR estimate) • Assume uncertainty of HR estimate is 20% of mean – no justification • Upper plausible estimate of leniolisib mortality used in HR calculation based on 1 expert opinion that survival curve should be closer to general population

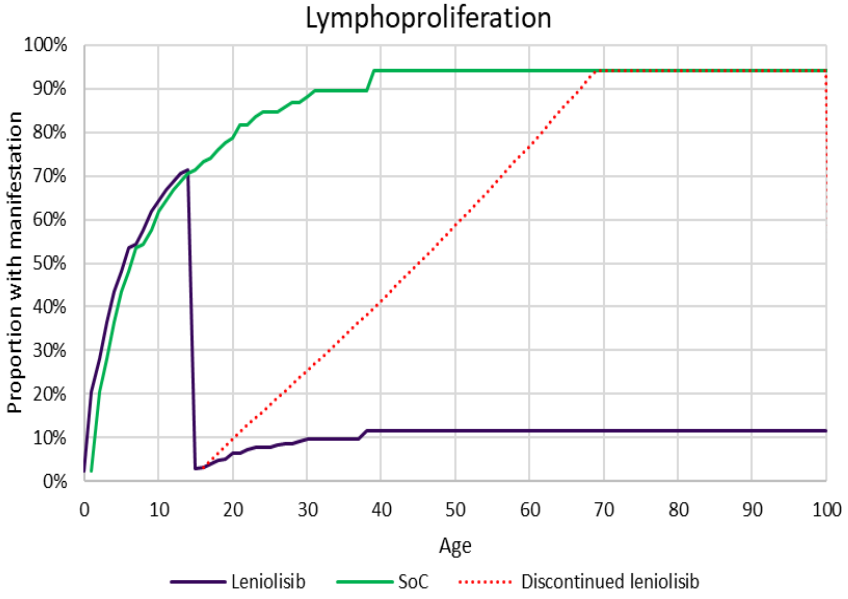
Abbreviations: KM, Kaplan-Meier; SLR, systematic literature review; HR, hazard ratio; EAP, early access programme

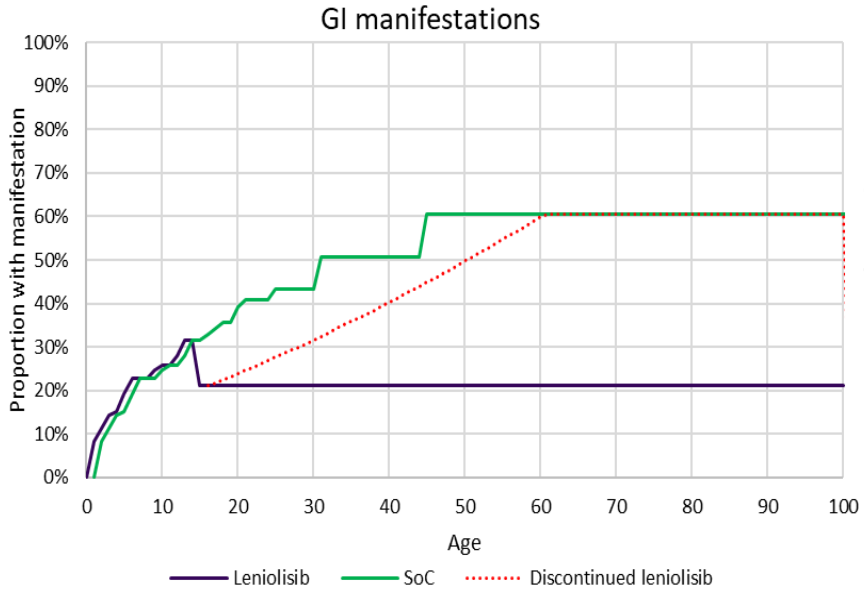
Key issue: Treatment discontinuation [3]

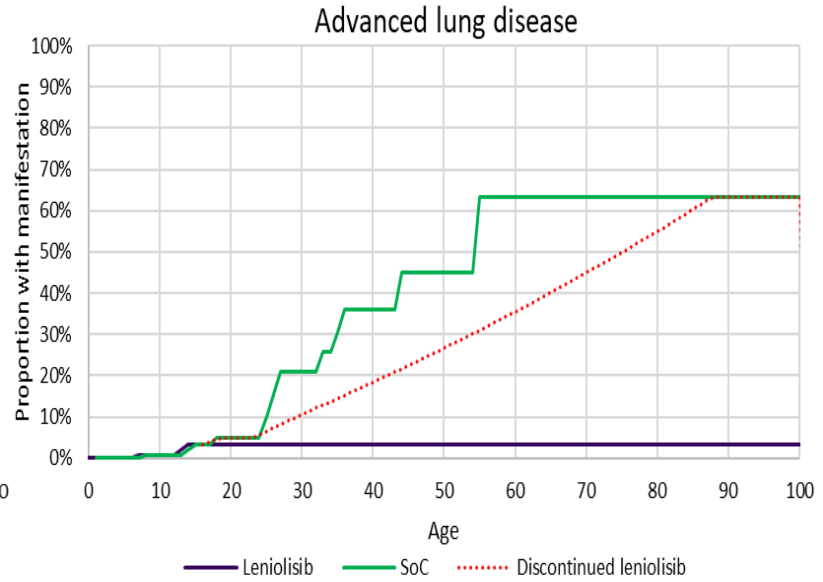
Impact of 100% discontinuation

Undiscounted LYG:
- SoC - [redacted] years
- Leniolisib – [redacted] years

Impact of discontinuation on modelled manifestations (3.54%)







Manifestations (age both groups achieve the maximum cumulative rate of manifestation)	Maximum manifestation rate in each group (A)	Age manifestation rate for "off Leniolisib" group (B)	Age maximum manifestation rate for SoC group (C)	Gap in years between groups (D) = B-C
Lymphoproliferation	93.95%	69	38	31
Gastrointestinal	60.64%	61	44	17
Cytopenias	28.62%	69	40	29
Infections	97.05%	43	43	0
Malignancies	61.77%	64	46	18
Advanced lung disease	63.38%	88	54	34
Hearing loss	25.62%	74	53	21

Abbreviation: SoC, standard of care; LYG, life years gained

HRQoL: utility values [1]

Emotional utility gain issue

No useable HRQoL data, reliant on proxy conditions for manifestation-related utility and expert opinion

Company

- Trial measured HRQoL with SF-36 (not EQ-5D), but not used in model:
  - Generic measure - cannot capture HRQoL benefits important for people with APDS
  - Lacked sensitivity in detecting meaningful changes in certain domains of SF-36
  - Baseline SF-36 data already includes impact of several APDS manifestations = overestimate APDS impact
  - Could not use utilities of individual manifestations/treatments due to complex combinations used
- No suitable APDS HRQoL studies, so utilities from proxy conditions or elicited from clinician EQ-5D vignette study
- Experts: expect a 72% improvement in days able to go to work / school if manifestations improved by 50%
  - Assume people on leniolisib with less severe manifestations have 50% reduction in manifestation disutility

Assumptions	Base case	Scenario	ICER impact
Baseline utility (no manifestations/ treatments)	Clinician EQ-5D: [redacted]	SF-36: [redacted]; Gen pop: [redacted]	Moderate
Leniolisib emotional benefit	0.1 (add to len baseline)	Exclude utility gain	Large
Manifestations / treatment use	Proxy condition literature and expert opinion	Clinician EQ-5D vignette	Small
Reduction for less severe disease	50%	25%	Moderate
Lower limit for utilities	No limit (0.106 lowest)	TTO study: 0.33; Clinician EQ-5D: -0.109	Large
Utility of multiple manifestations and treatments	Additive approach	-	Unknown

Abbreviations: ICER, incremental cost-effectiveness ratio; HRQoL, health-related quality of life; Gen Pop, general population; TTO, time trade off; len, leniolisib

HRQoL: utility values [2]

Manifestation inputs and modelled manifestations

Lack of long-term efficacy and QoL data is a concern, but unsurprising given rarity and small numbers affected

EAG:

- Acknowledge attempt to identify APDS HRQoL evidence but concerned these limitations pose challenges to validity and relevance of utility values used in model
  - Sympathetic to approach taken but emerging longer-term data is needed to address uncertainty
- Lack of data led to several assumptions which incorporated a high degree of uncertainty into analyses:

1. Additive approach to combine disutility for multiple manifestations may overestimate disutilities
   - If several similar manifestations affect same EQ-5D dimension, combined disutility may be lower than aggregated disutilities for individual manifestations
2. SF-36 estimates may be most applicable to model population
   - External validity issues associated with estimates from other sources
   - Acknowledge mapped SF-36 utility values not ideal and no other studies measuring APDS HRQoL
3. Utilities from proxy conditions:
   - Evidence suggests proxy respondents tend to overestimate impairment and underestimate HRQoL from condition – may provide inaccurate estimates of APDS HRQoL impact and complicate utility calculation
   - EQ-5D methods and non-UK value set were not used in calculation of some utility multipliers
   - Expert advisors did not respond regarding suitability of proxies - in absence of alternative evidence and expert views, EAG did not test this assumption in sensitivity analyses
4. Insufficient justification for the additional utility gain due to the emotional benefit of leniolisib (see issue 3)

Abbreviation: HRQoL, health-related quality of life; QoL, quality of life

Modelled manifestations and treatment use

1.5% discount rate issue

Company: some manifestations improve, but do not fully resolve with leniolisib

Estimates from company base case	On leniolisib	Off leniolisib (3.54% per year discontinue)	SoC
Proportion of people with manifestations (%)			
Lymphoproliferation	8.6	64.0	88.4
Gastrointestinal manifestations	20.2	50.0	51.8
Cytopenia	3.2	19.9	23.7
Infections	90.9	96.4	93.8
Malignancies	20.5	46.8	43.4
Bronchiectasis - associated airway disease	43.5	44.1	43.4
Advanced lung disease	3.1	32.0	38.3
Hearing loss	6.2	17.6	19.5
Proportion of people using treatment (%)			
Steriods	10.5	55.3	71.6
Immunoglobulin replacement therapy	37.9	69.0	69.3
HSCT	14.0	42.4	41.5
Tonsillectomy	45.5	52.2	50.3
Immunosuppressants	00.4	36.7	50.2

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Abbreviations: SoC, standard of care; HSCT, haemopoietic stem cell transplant

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.