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

For public – contains no confidential information

Technology appraisal committee HST [6 February 2024]

Chair: Paul Arundel

External assessment group: Newcastle University

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Company: Pharming Technologies

Leniolisib for APDS in people 12 years and over

- ✓ **Background, consultation responses and key issues**
- ❑ Modelling
- ❑ Other considerations
- ❑ Cost effectiveness
- ❑ Summary

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Background on APDS

RECAP

APDS is ultra-rare condition characterised by both immune dysregulation and immune deficiency

Causes

- APDS is caused by an overactive enzyme (a protein called PI3K delta) from mutations in APDS-relevant genes
- People with APDS may produce too few / many of some white blood cells 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

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
- APDS population is very heterogeneous, with large variation in diagnosis age, symptoms and severity

How does APDS progress over time?

- Disease onset can be variable over time in terms of age at presentation and complications
- As people age, the disease progresses, and people have more manifestations which can be more severe
- APDS manifestations often lead to premature death, survival studies estimate 68% alive at age 40

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

Leniolisib (Joenja®, Pharming)

Marketing authorisation	• **Indication (granted September 2024):** for the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and paediatric patients 12 years of age and older • Followed International Recognition Procedure.
Mechanism of action	• Leniolisib is a PI3K delta inhibitor that specifically lowers the activity of PI3K delta (i.e. reduces its ability to send signals), normalising PI3K 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

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

Preliminary recommendation and conclusion

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

Conclusions:

- Committee recalled uncertainties in the company's modelling and cost-effectiveness estimates
- Before a decision could be made about the most appropriate cost-effectiveness estimate, it considered that more exploration was needed of the:
  - modelling of treatment discontinuation
  - difference between the probabilistic and deterministic cost-effectiveness results.
- So, it did not recommend leniolisib for treating APDS in people aged 12 years and over.

ECM1 key issues

Issue	ECM1 conclusion	Resolved?
Treatment discontinuation	• 3.54% discontinuation rate most plausible to model • Further work needed to ensure rate of return of manifestations and treatment use is modelled appropriately	No
1.5% discount rate	• 3.5% discount rate should be used for health benefits and costs	No
Model uncertainty – PSA	• Want to know what factors were driving difference between deterministic and probabilistic cost-effectiveness estimates • Difference between estimates resolved during consultation	Yes
Uncertainties in key clinical trial	• Study 2201 part 2 was acceptable for decision making • Still unresolvable uncertainties in the evidence that should be considered in decision making	Yes
Lifelong treatment effect assumed	• Based on leniolisib's mechanism of action, a sustained long-term treatment effect is plausible	Yes
Utility gain from emotional benefit	• Additional utility gain should be removed from the model • Not seen enough evidence that modelled utility values did not capture hope, suggesting that it should be considered independently from effectiveness for APDS.	Yes

Abbreviations: PSA, probabilistic sensitivity analysis; ECM, evaluation committee meeting

Key questions for committee

Unresolved issues	ECM2 questions	ICER impact
Treatment discontinuation	• Which discontinuation rate is most appropriate: 3.54% or 2.7% per year? • Which method return to manifestation/treatment use risk is most appropriate?	Large
1.5% discount rate	• Is 3.5% discount rate still preferred for health benefits and costs?	Moderate
New issues raised at ECM2		
Survival modelling	• Should mortality be modelled as an APDS-specific mortality rate or a manifestation-specific mortality rate? • Has the model captured the impact of manifestations on survival appropriately?	Moderate
Other considerations		
Wider uncaptured benefits	• Are there any benefits of leniolisib that committee think have not been captured within the model? • E.g., Carer quality of life benefits, other clinical benefits not modelled, reduction in societal burden	Unknown

Abbreviations: SoC, standard of care; ICER, incremental cost-effectiveness ratio; ESID, European Society for Immunodeficiencies; ECM, evaluation committee meeting

Draft guidance consultation comments

Comments received from:

- **Immunodeficiency UK**
- **NHSE Immunology and Allergy Clinical Reference Group**
- **Company - Pharming**:
  - Draft guidance response
  - Revised base case: including updated model structure, discontinuation rate, discount rate, survival, manifestation hazard ratios, baseline utility
    - Unchanged: lifelong treatment effect assumed, probabilistic 10% standard error
    - Wider uncaptured benefits → removed treatment-related utility gain

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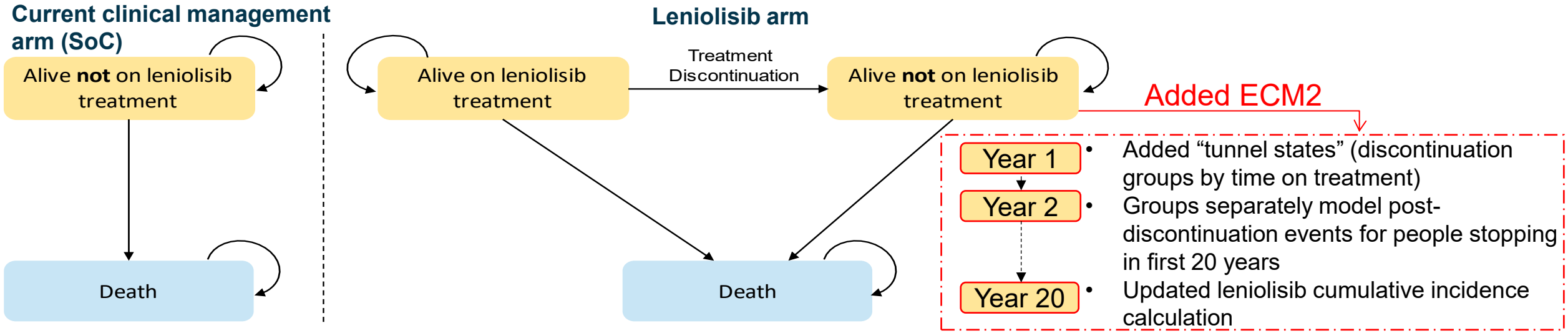
Company's ECM2 model

Abbreviations: SoC, standard of care; HR, hazard ratios; ESID, European Society for Immunodeficiencies; ECM, evaluation committee meeting



Changes since ECM1	ECM1	ECM2
Model structure	One discontinuation health state in leniolisib arm (alive not on treatment)	Discontinuation state includes 20 groups by time on treatment - shows different discontinuation cohorts per cycle
Discontinuation rate	3.54% per year	2.7% per year
Return to treatment use / manifestations	Average annual incidence rate of manifestations and treatment for SoC	Annual risk of developing manifestations returned to the annual risk of SoC at time of leniolisib initiation
Discount rate	1.5% (health benefits) and 3.5% (costs)	1.5% (costs and health benefits)
Baseline utility	[redacted]	[redacted]
Hazard ratios	Lymphoproliferation: HR 0.42; Malignancy: HR 0.55	Lymphoproliferation: HR 0; Malignancy: HR 0.53
Survival	Leniolisib: HR [redacted] SoC: survival data from literature case studies	Leniolisib: relative risk vs general [redacted] SoC: survival data from latest ESID registry dataset
Treated-related benefit	0.1 utility gain	Removed utilty gain. Focus on uncaptured benefits
Unchanged since ECM1: lifelong treatment effect assumed, 10% standard error for probabilistic model inputs		

Key issue: Treatment discontinuation [1]

ECM1 conclusions

Discontinuation rate: 3.54% per year considered most plausible to model

Manifestation and treatment recurrence rates

- Model: average annual incidence rate of SoC manifestations/treatment applied to discontinuation health state
  - ↳ Simplifying assumption to manage various risks for people who stop at different points, within same state
- How quickly return to SoC manifestations/treatment use rate depends on time on treatment, manifestation type and potentially, age at which started treatment
- Model structure did not allow exploration of assumptions → model produced results that lacked face validity
  - ↳ Work is needed to ensure rate of return post-discontinuation is modelled appropriately

Company response

Discontinuation rate: latest Study 2201 and EAP data = 2.7% per year (7 stopped, 291.9 patient-years)

Manifestation and treatment recurrence rates

- Limited data to inform estimates of post-discontinuation risk of manifestation recurrence and treatment use
- *Revised model*: "Alive on SoC" discontinuation health state replaced by 20 different "tunnel states"
- Experts expect leniolisib to stabilise irreversible organ damage e.g., hearing loss → people more likely to maintain better overall health, so disease progression post-discontinuation would start from healthier state

Abbreviations: EAP, early access programme; SoC, standard of care; ECM, evaluation committee meeting

Key issue: Treatment discontinuation [2]

Company response continued

Clinical expert opinion on plausibility of committee suggested discontinuation scenarios:

1. *Adjustment of hazards for duration of treatment*
   - Most plausible long-term effect = leniolisib stops manifestation development but at risk again if discontinue
   - 1 expert: risk may return to that of younger person after 5-10+ years of treatment
   - Not plausible for people on treatment 10+ years to return to lifetime risk / SoC rates
2. *Reduced hazards reflecting lower risks in older people*
   - Not considered plausible – most experts thought risk of developing manifestations increases with age
3. *Immediate return to SoC rates*
   - Scenario not modelled as considered clinically implausible given immune system changes take years
   - ECM1 experts = may take several months / years to recur to SoC manifestations/treatments
4. *Revert to annual incidence of each manifestation from birth*
   - Not considered likely, but 1 expert thought for people treated for 5-10+ yrs it was plausible for long-term manifestations (bronchiectasis, advanced lung disease, and malignancy)
   - Some thought the longer stay on treatment = less likely manifestations will return

Abbreviations: SoC, standard of care; ECM, evaluation committee meeting

Key issue: Treatment discontinuation [3]

Company response continued

Company scenario analyses:

- *Base case: return to SoC risks before starting leniolisib (e.g., age 15), regardless of age and time on treatment*
  - Considered most clinical plausible by clinical experts
- *Scenario 1: return to SoC risks equal to age which discontinue (e.g., stop age 20, next cycle risk of 21 yr old)*
- *Scenario 2: return to risks of newborn (for long-term manifestations) and SoC risks for other probabilities*
- *Scenario 3: return to SoC lifetime risk - apply catch up function, equal to time on treatment*
  - E.g., 2 years on treatment = return to SoC prevalence within 2 years
  - Catch up function temporarily applies annual risk higher than in SoC to return to SoC prevalence
  - Applied to those treated <10 years. If 10+ years treatment, return to risk of starting age (base case)

EAG comments

Discontinuation rate: 2.7% discontinuation rate based on new real-world evidence is plausible

Manifestation and treatment recurrence rates

- Acknowledge company's attempt to address concerns and approaches taken are generally appropriate
- Original model calculation of the cumulative incidence for leniolisib was incorrect
- New model checked by senior modeller - found no errors with the implementation of discontinuation but there is likely errors in the cumulative incidence calculations after discontinuing leniolisib
  - Errors not corrected as identified at late stage, but do not expect this to have significant impact on results
  - But there was an uncertainty regarding how the manifestation hazard ratios were calculated

Abbreviations: SoC, standard of care

Key issue: Treatment discontinuation [4]

EAG comments continued

- Face validity concerns (sustained QALY benefit after 100% discontinuation in 1st year) persist when exploring model assumptions in company base case approach and scenarios 1 and 2 (scenario 3 addresses this issue)
  - E.g., base-case extreme scenario → 20+ yrs to return to SoC lymphoproliferation rate and [redacted] QALY gain
- Sustained QALY benefit issue depends on assumptions of [1] disutility values; [2] returning rates, not errors
  - Intuitive that QALY benefit disappears if assume immediate return and sustained if assume gradual return

1. Sustained QALY benefit amplified by large disutilities for some manifestations e.g., gastrointestinal
   - These disutilities diminish or disappear when people on leniolisib - contribute to sustained QALY benefit when people gradually return to have manifestations upon treatment discontinuation
2. Clinical expert evidence suggests that returning to risk before leniolisib initiation (company's base case) is most plausible scenario and returning to lifetime risk (scenario 3) is the least plausible scenario
   - Scenario 3 implies "catch-up" risks higher than SoC manifestation risks of the same age in first few years after discontinuation, which is against the expert views submitted by company

- Given available evidence presented, EAG think company base case approach is most plausible
  - No clinical evidence or opinion obtained by EAG during consultation due to time constraints

1. Which discontinuation rate is most appropriate to model – 3.54% or 2.7% per year?
2. Which method return to manifestation/treatment use risk is most appropriate?

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

Graph showing manifestation-specific mortality rate scenarios

New Issue: Survival modelling

ECM1

- SoC survival: Weibull distribution fit to survival data from published case studies (APDS-specific mortality rate)
- Company ran manifestation-specific mortality rates scenario – predicted survival much lower than case study
  - Used [redacted] calibration factor to align SoC survival curve with observed mortality in people with APDS
- Leniolisib survival: applied HR for survival of [redacted] assumed based on clinical expert opinion

Company DG response

- Updated base case: Weibull distribution fit to survival data from latest ESID registry dataset (November 2024)
  - ↳ Latest data suggests survival was originally overestimated. Estimates were also subject to bias
  - ↳ Survival likelihood for people treated with leniolisib vs general population [redacted]% (relative risk: [redacted])

EAG comments

- Base case: align with company → ESID is an appropriate source, and estimates are potentially less biased
- Concerned that mortality in company's model is modelled independently of manifestation risk
  - People with more manifestations should have higher mortality rates, which is not reflected in model
  - Any scenario that changes the risk of manifestations should also affect model survival predictions
- EAG explored impact of manifestation-specific mortality rates alongside different manifestation risk scenarios
- Calibrated model ([redacted] calibration factor), so survival curve closely matches early part of SoC curve
  - However, rates estimated based on HRs from single study using proxy disease so not used in base case

Should mortality be modelled as an APDS-specific mortality rate or a manifestation-specific mortality rate? Has the model captured the impact of manifestations on survival appropriately?

Abbreviations: SoC, standard of care; ESID, European Society for Immunodeficiencies; HR, hazard ratios; SLR, systematic literature review

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

ECM1 conclusions: 3.5% should be used for costs and health effects

NICE 1.5% discount rate criteria	Met?
The technology is for people who would otherwise die or have a very severely impaired life	No
It is likely to restore them to full or near-full health	No
The benefits are likely to be sustained over a very long period	Yes

Company DG response

Updated base case uses a 1.5% annual discount rate for health benefits and costs

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

Likely most people have manifestations prior to diagnosis

- Acknowledge APDS is heterogeneous - familial testing can diagnose before symptoms in minority
- UK data suggests ~7 yr delay between average age of first symptom (2 years) and diagnosis age (9.2 yrs)
- By age 10 >90% had severe manifestation → only minority diagnosed not had manifestations by age 12

Regardless of severity at diagnosis, all with APDS progress to have significantly reduced QoL and life expectancy

Survival: latest ESID data (Nov 2024): indicates 25% mortality by age 21 and median survival of 44 years

- Survival estimates likely overestimated and UK experts suggest mortality significantly underreported

QoL: almost all people with APDS have severe or significant disease → by age 46, 63% ≥ 1 severe manifestation

- Explains why only 31% of IDUK survey respondents reported satisfaction with their QoL

Abbreviation: ESID, European Society for Immunodeficiencies; QoL quality of life

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

Modelled manifestation and treatment use

Company DG response continued

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

- Clinicians and RWE: expect leniolisib to alleviate manifestations impact → restoring most to full / near-full health
  - 2 cases highlight transformative potential of leniolisib for people with severe APDS, restoring full health
- Most experts agreed short-term immune reconstitution could translate into long-term immune competence
  - HST7 (ADA-SCI): committee reassured this translation would enable return to full/near full health
- Leniolisib allows most severe patients to go work/school, improves QoL, minimises manifestation development
- Although some damage is irreversible, stopping progression and reversing some aspects offers huge QoL value
- Treatment starts age 15 and benefits last lifetime – important to avoid diminishing future leniolisib health gains

EAG comments

- Base case: 3.5% discount rate for both costs and health benefits
- HST7 conclusion: committee uncertain whether Strimvelis fully met criteria to use 1.5% discount rate
- Evidence suggests some people could return to near full health (likely those at early APSD stage), but larger sample of people restored needed to strengthen claim

Other considerations

- HST criteria 3: uncertainty about extent that 'APDS reduces quality and length of life' would apply to all people with ADPS because of condition heterogeneity and small amounts of available evidence

Does committee still consider that a 3.5% discount rate is most appropriate for this evaluation?

Abbreviation: HRQoL, health-related quality of life; RWE, real world evidence; ADA-SCI, adenosine deaminase deficiency–severe combined immunodeficiency

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Uncaptured benefits

Substantial benefits of leniolisib not reflected in QALY gain now that treatment-specific utility removed

Leniolisib expected to improve key manifestations not included in the model

- E.g., Fatigue, arthritis, short stature, depression, energy levels, memory impairment, neurodevelopmental concerns

Leniolisib increases hope, improves QoL and reduces disease burden, social isolation and emotional distress

- IDUK survey: report feelings of loneliness, frustration and hopelessness for future and anxiety about progression

Leniolisib has benefits relating to society, education, and inequality

- *Societal:* reduction in hospitalisations is likely to significantly reduce the societal costs associated with APDS
- *Education/social life*: EQ-5D does not capture long-term impact of falling behind academically and socially
- *Inequality:* offers alternative for people from ethnic minority backgrounds that report difficulty finding HSCT donor

Leniolisib expected to provide caregiver QoL benefits (includes comments from Immunodeficiency UK)

APDS significantly impacts carers physical and mental health, QoL and ability to work and live an unrestricted lifestyle

- Stress, anxiety, depression, difficulty sleeping, feeling isolated, fears about future - '*I'm worried all the time*.'
- Inability to keep job = financial instability (*4/7 said APDS hinders carer employment and causes financial strain*)
- Adults with APDS may be caring for children with APDS → need to manage own health and caring duties

Leniolisib expected to reduce burden on caregivers, and so decrease loss of income and productivity

- Physicians and caregivers agreed that leniolisib would have a significant positive impact on caregiver QoL
- *'Having the chance to try medication gives us that bit of hope that she will one day be healthier than she is today'*

Abbreviations: QoL, quality of life; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant

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)	18.01
Company base case (probabilistic)	18.18
EAG base case (deterministic)	18.01
EAG base case (probabilistic)	17.96

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

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

Equality considerations

RECAP

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

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Cost-effectiveness assumptions and results

Assumption	Company base case	EAG base case
Discount rate	1.5% for health effects and costs	3.5% for health effects and costs
*Note: EAG use different updated unit costs to company, unchanged from ECM1		

Company base case scenario	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
Return to manifestation rate scenario 1	↓	↑	Over £100,000
Return to manifestation rate scenario 2	↓	↑	Over £100,000
Return to manifestation rate scenario 3	↑	↓	Over £100,000
3.5% 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; ECM, evaluation committee meeting

Additional cost-effectiveness scenarios

Additional cost-effectiveness scenarios	Inc costs	Inc QALYs	ICER (£/QALY)
Company base case (deterministic)	See part 2	See part 2	Over £100,000
Baseline utility: EQ-5D clinician survey	↔	↓	Over £100,000
Survival data source: case series (ECM1 data)	↓	↓	Over £100,000
EAG base case (deterministic)*	See part 2	See part 2	Over £100,000
Manifestation-specific mortality rates	↓	↓	Over £100,000
Discontinuation scenario 1: SoC risk at age at which discontinue	↓	↑	Over £100,000
Discontinuation scenario 2: newborn risk / SoC risk	↓	↑	Over £100,000
Discontinuation scenario 3: return to SoC lifetime risk	↑	↓	Over £100,000
Manifestation-specific mortality rates and discontinuation scenario 1	↓	↓	Over £100,000
Manifestation-specific mortality rates and discontinuation scenario 2	↓	↑	Over £100,000
Manifestation-specific mortality rates and discontinuation scenario 3	↓	↓	Over £100,000
HR (lymphoproliferation) = 0.42; HR (malignancy) = 0.55	↑	↓	Over £100,000
* EAG scenarios also produced using 1.5% discount rate in part 2 slides. All ICERs above £100,000 per QALY gained.			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; HR, hazard ratio; SoC, standard of care; ECM, evaluation committee meeting; ESID; European Society for Immunodeficiencies

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Key issues and considerations

Issues / considerations	ICER impact
Treatment discontinuation	Large
Survival modelling	Moderate
1.5% non-reference case discount rate	Moderate
Uncaptured benefits	Unknown

Abbreviations: ICER, incremental cost-effectiveness ratio

Leniolisib for APDS in people 12 years and over

Supplementary appendix

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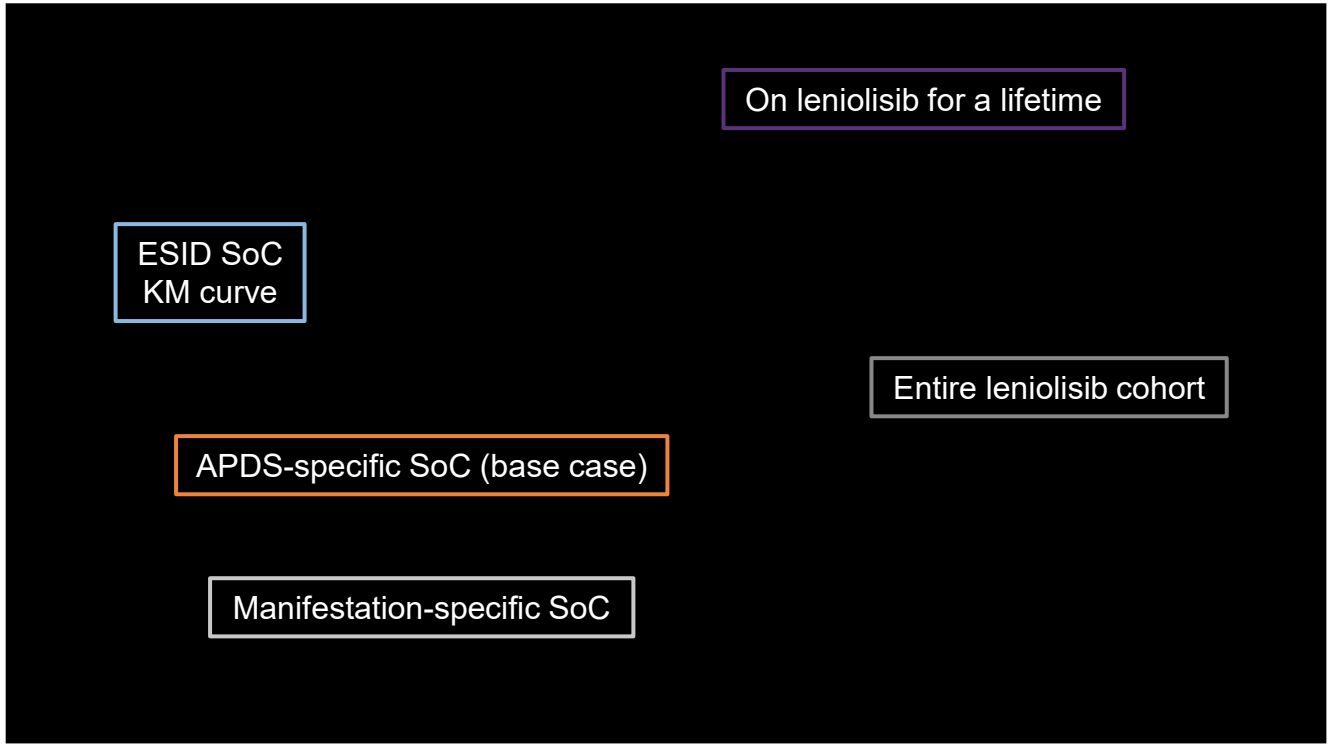
Survival modelling issue

Manifestation-specific mortality rate scenarios

Model survival curves for leniolisib assuming fixed cohort survival and manifestation-specific mortality rates

Survival Curves	Manifestation-specific mortality rates applied to different manifestation scenarios	Inc undisc QALYs
Leniolisib: base case	Return to starting age manifestation risk	15.55
Leniolisib: scenario 1	Current age SoC manifestation risks	15.66
Leniolisib: scenario 2	Return to newborn manifestation risks for long-term conditions and current age SoC manifestation risks for other manifestations	18.60
Leniolisib: scenario 3	Catch-up to SoC cumulative manifestation incidence based on duration of treatment	14.72



- Manifestation-specific SoC survival curve may overestimate survival in short-term and underestimate survival in the long-term
- Leniolisib model survival curves were assumed to vary if manifestation risk and incidence curves varied in scenario analyses
  - Leniolisib survival curves do not vary significantly between scenarios.
- Scenario 2 associated with most favourable survival curve - malignancies and advanced lung disease associated with greatest mortality and have a higher risk at older ages

Abbreviations: ESID, European Society for Immunodeficiencies; KM, Kaplan Meier, QALYs, quality-adjusted life years; SoC, standard of care

Modelled manifestations and treatment use

1.5% discount rate issue

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

Estimates from company revised base case	On leniolisib	SoC
Proportion of people with manifestations (%)		
Lymphoproliferation	2.93	88.89
Gastrointestinal manifestations	21.04	50.86
Cytopenia	3.33	23.06
Infections	94.92	95.19
Malignancies	24.06	38.23
Advanced lung disease and bronchiectasis	59.90	80.10
Hearing loss	6.97	18.36
Proportion of people using treatment (%)		
Steriods	10.35	69.84
Immunoglobulin replacement therapy	39.08	68.57
HSCT	14.61	39.04
Tonsillectomy	47.60	50.86
Immunosuppressants	0.00	48.13
Note: Table shows the proportion of people with manifestations but does not show the number of manifestation events e.g., the number of infections experienced. Please see model for this information.		

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

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

ECM1 uncaptured benefits

ECM2 uncaptured benefits

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