Poster

HTA280

Evidence Generation for APDS: Multi-Method Collection of Expert Judgement to Inform UK Health Technology Assessment for an Ultra-Rare Condition

Joanne Beatrice Tutein Nolthenius,[1] Rebecca Beale,[2] Laura J Clark,[3] Manya Mirchandani,[2] John Whalen[1]

[1]Pharming Group N.V., Leiden, Netherlands; [2]Costello Medical, London, UK; [3]Costello Medical, Manchester, UK

OBJECTIVE

To employ a robust, multi-method framework consisting of a modified structured expert elicitation (SEE) exercise, qualitative surveys and quantitative surveys to address evidence gaps and validate assumptions to inform the cost-effectiveness model (CEM) for the health technology assessment (HTA) of leniolisib.

BACKGROUND

- Activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) is an ultra-rare and complex inborn error of immunity (IEI) affecting 1–2 per million people and first recognised in 2013.[1,2]
- APDS is characterised by immune deficiency and immune dysregulation, with multi-system clinical manifestations including lymphoproliferation, enteropathy, advanced lung disease and malignancy.[3,4]
- Due to the rarity and evolving understanding of APDS, evidence on its natural history is sparse, increasing uncertainty for decision-making in HTA and for cost-effectiveness analysis.
- Leniolisib is an oral, small molecule inhibitor approved in the UK in 2024 for the treatment of APDS in adult and paediatric patients 12 years of age and older.[5] Leniolisib demonstrates disease-modifying activity in APDS through direct targeting of the causative pathway, normalisation of immunophenotype and improvement of clinical manifestations.[6–8]
To address evidence gaps and validate assumptions for cost-effectiveness modelling and HTA submissions, expert judgement was collected.

METHODS

- Twelve APDS clinical experts, nine of which had direct experience treating patients with leniolisib, were recruited from the UK, Europe and Canada, and completed five exercises in total (**Figure 1**). Example questions are presented in **Figure 2**.
  - **Exercise 1**: Four clinical experts completed a modified SEE exercise. The SEE was carried out in line with best practices,[9–11] including the provision of training slides and an evidence dossier prior to completion of the exercise.
  - The SEE comprised of two surveys:
    - **Part 1**: clinical experts were presented with Kaplan-Meier (KM) data for manifestations and survival in patients receiving standard of care (SoC).[4,12] Based on their own experience, they were asked to provide estimates at different timepoints for the occurrence of each manifestation and select the most plausible survival curves representing manifestation occurrence and mortality.
    - **Part 2**: clinical experts were presented with KM point estimates and/or the aggregated results from the first survey and were asked to estimate the impact of leniolisib on manifestation occurrence and survival at the same timepoints as Part 1.
  - **Exercise 2**: Four clinical experts completed EQ-5D-5L to generate utility values for APDS health-state vignettes.[13] These vignettes were developed through interviews with people with APDS and the published literature, and validated by clinical experts, to represent manifestations frequently experienced by people with APDS.
  - **Exercise 3**: Five clinical experts completed the qualitative survey, answering a mixture of yes/no and 5-point scale questions, validating key assumptions for the CEM and identifying proxy conditions.
  - **Exercise 4**: Five clinical experts completed the quantitative survey, estimating healthcare cost and resource use (HCRU) associated with the treatment of APDS.
  - **Exercise 5**: Six clinical experts estimated risk of manifestation recurrence post-discontinuation of leniolisib, in response to questions from the National Institute for Health and Care Excellence (NICE) Committee.

RESULTS

- All 5 exercises contributed towards robust, expert-driven data to validate assumptions and address evidence gaps in the CEM, supporting patient access in the UK.
  - **Exercise 1** results consisted of means, standard deviations, medians and upper and lower plausible limits of APDS manifestation incidence and mortality, alongside best-fit KM curves for manifestation occurrence and mortality. This enabled calculation of hazard ratios (HR) comparing leniolisib with SoC (**Figure 3**).
  - **Exercise 2** generated utility values, providing the impact of APDS on HRQoL and validating the utility values used in the CEM.
  - **Exercises 3 and 4** generated consensus on a range of questions related to clinical manifestations, treatment limitations and HCRU.
  - **Exercise 5** contributed to consensus on the most likely risk of manifestation recurrence post-discontinuation of leniolisib.

Figure 1. Summary of recruited experts, methods and results obtained

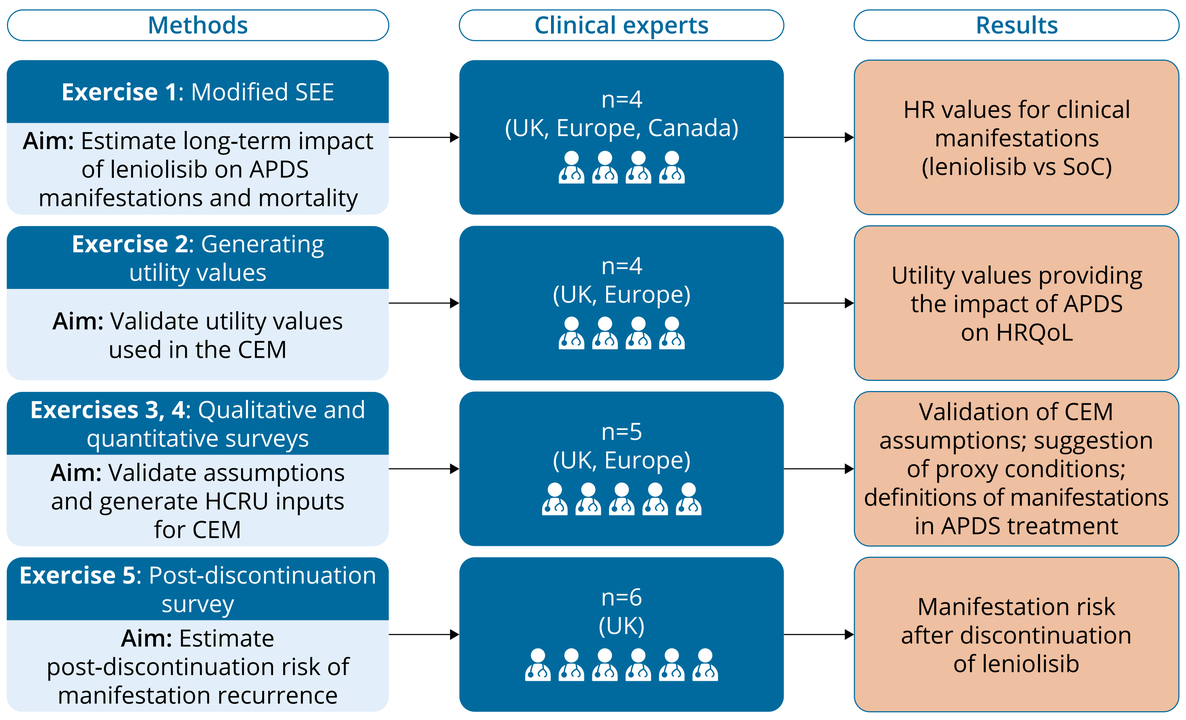


Figure 2. Example questions from Exercises 1, 3 and 4

Data provided to participants | For participants to complete

Exercise 1: Modified SEE

	For patients aged 12 years without lymphoproliferation, what is the 3-year risk of developing lymphoproliferation on SoC vs leniolisib?	
	SoC	Leniolisib
European registry point estimate[4]	9.7%	NA
Lower plausible limit	0%	
Upper plausible limit	22.7%	
Please put an 'X' in the box if you feel particularly uncertain about answering the question		

Exercise 3: Qualitative Survey

To what extent do you agree that a reduction in lymphproliferation (as measured by radiological measures of lymphadenopathy and splenomegaly) could be associated with a reduced risk of developing lymphoma?				
Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree

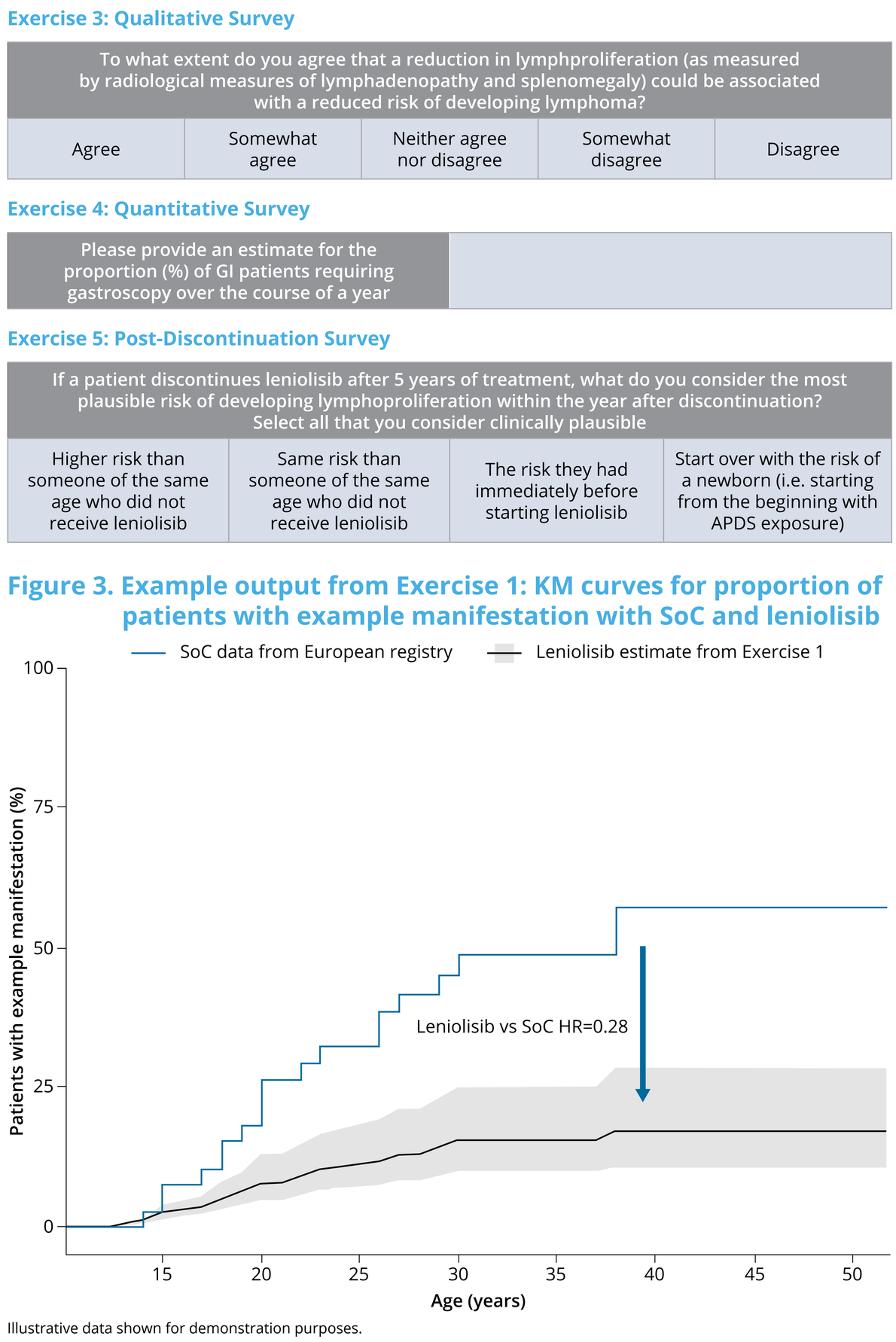
Exercise 4: Quantitative Survey

Please provide an estimate for the proportion (%) of GI patients requiring gastroscopy over the course of a year	

Exercise 5: Post-Discontinuation Survey

If a patient discontinues leniolisib after 5 years of treatment, what do you consider the most plausible risk of developing lymphoproliferation within the year after discontinuation? Select all that you consider clinically plausible			
Higher risk than someone of the same age who did not receive leniolisib	Same risk than someone of the same age who did not receive leniolisib	The risk they had immediately before starting leniolisib	Start over with the risk of a newborn (i.e. starting from the beginning with APDS exposure)

Figure 3. Example output from Exercise 1: KM curves for proportion of patients with example manifestation with SoC and leniolisib



Illustrative data shown for demonstration purposes.

CONCLUSIONS

When conventional evidence sources are limited, as in ultra-rare conditions like APDS, expert-informed evidence generation can support HTA. This study demonstrates how multi-method approaches can address evidence gaps, validate model assumptions and inform decision-making, ultimately facilitating patient access in rare conditions.

REFERENCES: **1.** Vanselow et al. Front Immunol 2023;14:1208567; **2.** Angulo et al. Science 2013;342(6160):866–871; **3.** Elkaim et al. J Allergy Clin Immunol 2016;138:210–218.e9; **4.** Maccari et al. Clin Immunol 2026;283:110632; **5.** MHRA approves first medicine for rare immune disease APDS. 2024; **6.** Rao VK. et al. J Allergy Clin Immunol 2023;44:34; **7.** Rao et al. Blood 2017;130:2307–2316; **8.** Rao et al. Blood 2024;141:971–983; **9.** Bojke et al. Health Technol Assess 2021;25:1–124; **10.** Horscroft et al. Structured expert elicitation for healthcare decision making: An overview; **11.** Horscroft et al. Structured expert elicitation for healthcare decision making: A practical guide; **12.** Hanson et al. Clin Exp Med 2024;24:17; **13.** Tutein Nolthenius et al. Adv Ther 2025;42:4048–4066.

ABBREVIATIONS: APDS: activated PI3K delta syndrome; CEM: cost-effectiveness model; HCRU: healthcare cost and resource use; HR: hazard ratios; HRQoL: health-related quality of life; HTA: health technology assessment; IEI: inborn error of immunity; KM: Kaplan-Meier; NICE: National Institute for Health and Care Excellence; PI3K: phosphoinositide 3-kinase; SEE: structured expert elicitation; SoC: standard of care.

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