CO12

APDS treatment in Germany: Decision criteria, costs and contribution of Leniolisib to outcomes

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1. BACKGROUND / OBJECTIVES

Activated PI3 Kinase Delta (PI3Kδ-) Syndrome (APDS) is a rare genetically defined inborn error of immunity (IEI), that was first recognized in 2013.[1-3] APDS affects less than 1-2 individuals per 1,000,000 worldwide. It is associated with lifelong morbidity and premature mortality. The highly variable disease manifestations – with both immunodeficient and immunodysregulatory features – mostly have a paediatric onset.[4-6]

Leniolisib – a potential new therapeutic precision agent – is an oral, targeted phosphoinositide 3-kinase delta (PI3Kδ) inhibitor that is indicated for the treatment of APDS. It targets specifically the underlying pathophysiology of the condition and modifies the disease progression of APDS.

To better classify the contribution of leniolisib in the therapy of APDS patients medically relevant decision criteria in Germany were assessed upon which a model was built.

2. METHODS

The model focuses on decision criteria in the treatment of APDS in Germany and their medical and economic impact. For the present study key decision outcomes were the primary focus to model disease impact.

Data on the treatment of APDS in Germany was collected through two online surveys and two roundtable discussions. After initial pre-surveys the aggregated results were discussed with all participants. Six medical experts from the German health care system with experience in treating and/or researching APDS participated. A MaxDiff analysis – a conjoint analysis method for ranking people's preferences by asking them multiple times to choose the best and worst option from a group of statements[7] – was conducted in November 2024 and March 2025 to assess criteria for treatment value. Based on expert responses, a counting score for 'most important' was calculated for APDS. Due to questions raised in the first roundtable, the second survey included clarifications on "efficacy of therapy" and "therapeutic impact". To determine value in the treatment of APDS, similar analyses using comparable methods have already been conducted in other countries, namely in Spain[8,9], which were considered establishing the items for MaxDiff analysis.

In addition to the value determination, in the second online survey and subsequent roundtable discussion (03/2025), infections and other manifestations of APDS were compared between standard of care (SOC) and the treatment with leniolisib. Finally, mortality of APDS patients was investigated. Accordingly, using structured expert elicitation the aim was to generate plausible estimates for the long-term impact of leniolisib on APDS manifestations and mortality.

The standard of care (SOC) of treatment patterns and outcomes was informed by Kaplan-Meier data that were produced using individual patient data taken from the European Society for Immunodeficiencies (ESID) APDS registry[10]. This registry contains data from patients with APDS collected from a retrospective investigation and it provides estimates for the occurrence of APDS manifestations for people treated with currently available SOC. Results of a UK cost-effectiveness model of leniolisib were also taken into account.[11]

Based on the ESID outcomes data, the six participating medical experts were asked to provide estimates for upper and lower limits for the occurrence of manifestations and mortality for patients treated with current SOC. Different approaches were taken to elicit the required data, specific to each manifestation.

3. RESULTS

Infections

APDS patients typically present with respiratory tract infections (RTI) and other types of infections.[12-14] According to the experts surveyed, the average number of infections under SOC is 5,2 per year (respiratory infections) and 3,4 per year (other types of infections), respectively. Even if infections cannot be completely avoided, the assessment is that leniolisib can significantly reduce their number, especially in APDS1 patients, It is assumed that under leniolisib, the average number of infections per year is reduced to 2,5 (respiratory infections) and 1,5 (other types of infections; see **Figure 1**). Leniolisib can make an important contribution to keeping infections to a minimum and thus improving patients' quality of life.[15-17]

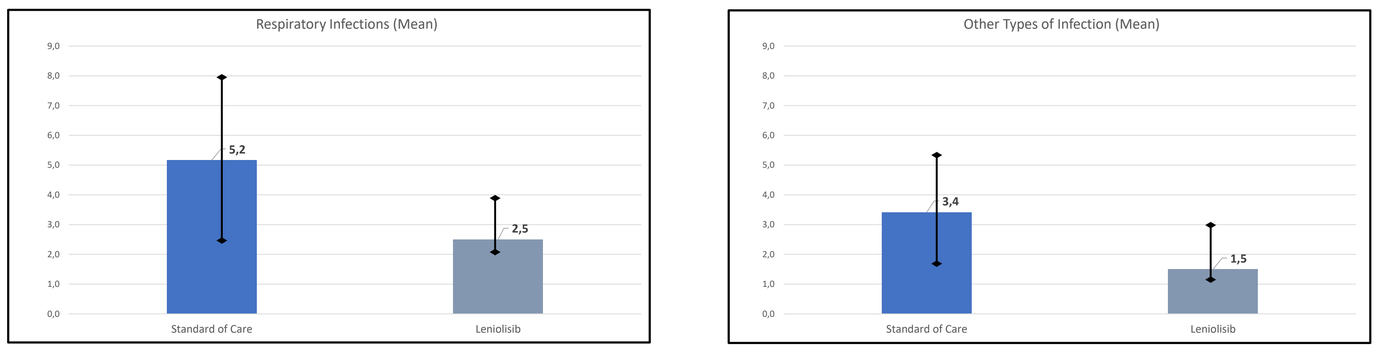


Figure 1: Number of infections per year (Mean): Standard of Care vs. Leniolisib estimate

Mortality

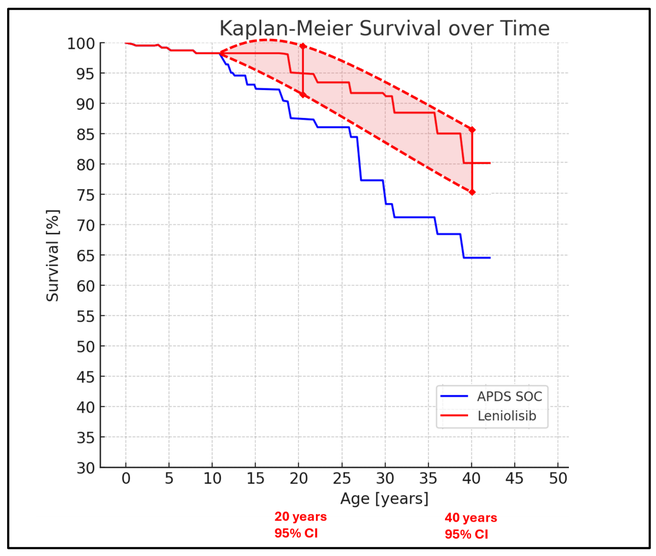
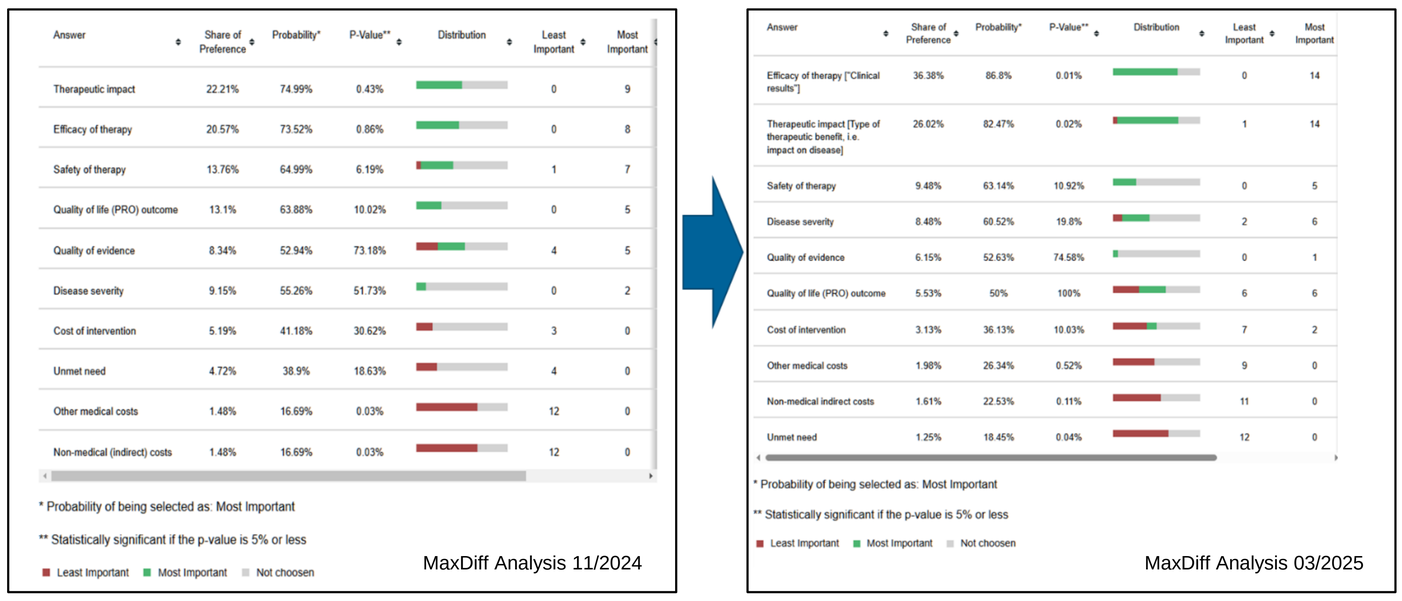


Figure 2: Mortality in APDS: Standard of Care vs. Leniolisib treatment

The experts surveyed expect leniolisib to have positive effects on infections and other manifestations of APDS, albeit to varying degrees. To date, no comparative clincial long-term experience with leniolisib is available, which is why the long-term effects cannot yet be substantiated with study data – especially regarding mortality. Despite available SOC treatments, life expectancy for patients with APDS is shortened from the average lifespan. The experts surveyed assume that leniolisib can significantly increase the life expectancy of APDS patients. A reduction in mortality is the cumulative consequence of the positive effects of leniolisib on APDS manifestations (see **Figure 2**).

Determining value in the treatment of APDS in Germany

The MaxDiff analysis showed that "efficacy of therapy" and "therapeutic impact" are ranked consistently in both analyses as the most important criteria to determine value of a new therapy for APDS patients in Germany (see **Figure 3**). "Safety of therapy" is also seen consistently as the second important criterion. Overall, results of the second survey (03/2025) were well consistent to the first survey (11/2024), especially regarding the most important decision criteria. This confirms the reliability of the results: a (new) therapy primarily must be effective and safe. Of note, for the most relevant criteria also highly homogeneous results between the participating experts were recorded.



MaxDiff Analysis 11/2024

Answer	Share of Preference	Probability*	P-Value**	Distribution	Least Important	Most Important
Therapeutic impact	22.21%	74.99%	0.43%		0	9
Efficacy of therapy	20.57%	73.52%	0.86%		0	8
Safety of therapy	13.76%	64.99%	6.19%		1	7
Quality of life (PRO) outcome	13.1%	63.88%	10.02%		0	5
Quality of evidence	8.34%	52.94%	73.18%		4	5
Disease severity	9.15%	55.26%	51.73%		0	2
Cost of intervention	5.19%	41.18%	30.62%		3	0
Unmet need	4.72%	38.9%	18.63%		4	0
Other medical costs	1.48%	16.69%	0.03%		12	0
Non-medical (indirect) costs	1.48%	16.69%	0.03%		12	0

* Probability of being selected as: Most Important

** Statistically significant if the p-value is 5% or less

Least Important Most Important Not choosen

MaxDiff Analysis 03/2025

Answer	Share of Preference	Probability*	P-Value**	Distribution	Least Important	Most Important
Efficacy of therapy ["Clinical results"]	36.38%	86.8%	0.01%		0	14
Therapeutic impact [Type of therapeutic benefit, i.e. impact on disease]	26.02%	82.47%	0.02%		1	14
Safety of therapy	9.48%	63.14%	10.92%		0	5
Disease severity	8.48%	60.52%	19.8%		2	6
Quality of evidence	6.15%	52.63%	74.58%		0	1
Quality of life (PRO) outcome	5.53%	50%	100%		6	6
Cost of intervention	3.13%	36.13%	10.03%		7	2
Other medical costs	1.98%	26.34%	0.52%		9	0
Non-medical indirect costs	1.61%	22.53%	0.11%		11	0
Unmet need	1.25%	18.45%	0.04%		12	0

* Probability of being selected as: Most Important

** Statistically significant if the p-value is 5% or less

Least Important Most Important Not choosen

Figure 3: Determining value in the treatment of APDS in Germany: MaxDiff Analysis 11/2024 vs. 03/2025

4. CONCLUSION

Decision criteria of German physicians for treating APDS are well in line with other therapeutic areas, with efficacy and safety considered to be most relevant.

Based on data on leniolisib available today, mortality and several patient-relevant morbidity endpoints are expected to improve in future clinical practice in Germany and leniolisib may also significantly modify the course of disease in APDS patients.

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