Comparative analysis of medicines reimbursement in France : rare diseases versus other conditions

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CONTEXT

In Europe, a disease is considered rare if it affects fewer than one in 2,000 people[1]. To date, nearly 7,000 rare diseases have been identified, impacting over 3 million patients in France[2]. Access to medicines can be particularly challenging for these patients, with only 5% of rare diseases having a specific treatment approved[3]. As a result, rare diseases pose a major public health challenge, with a pressing need for effective therapies.

OBJECTIVE

The objective of this analysis was to assess the impact of the disease rarity on the Transparency Committee (TC) evaluation for reimbursement eligibility.

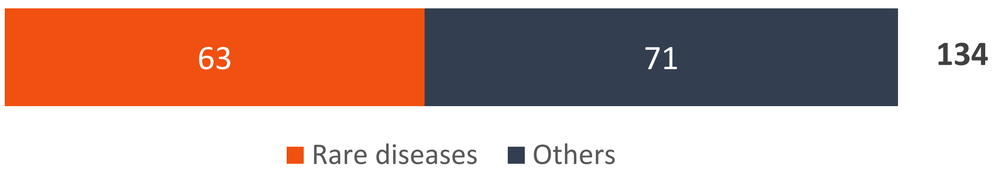
METHOD

- We conducted a comparative analysis based on the **opinions issued by the TC in 2021 and 2022 for which a clinical added value (ASMR) I to IV has been granted.** Only new registrations and extensions of indication were considered in the analysis.
- For a given drug, when several ASMR levels have been granted in the same opinion, each ASMR has been considered as a TC evaluation. A single TC opinion may therefore correspond to several evaluations.
- Two groups were considered for the comparative analysis: **rare disease evaluations versus other evaluations**. The identification of rare diseases was based on the National Data Bank on Rare Diseases (BNDMR)[4].
- Several variables were compared between the two groups, including clinical development and its assessment by the TC, as well as clinical benefit (SMR) and ASMR levels granted.

RESULTS

- A total of 129 TC opinions meeting the inclusion criteria were selected, resulting in an analysis sample of **134 evaluations in total**.
- Among them, nearly half (n = 63; **47%**) involved a **rare disease** of which the majority (n = 39 ; 62%) of drugs were granted orphan designation.

FIGURE 1. Distribution of the 134 TC evaluations included in the analysis



A. Clinical data

- The methodology of the study with the highest level of evidence for each evaluation was collected and results are summarized in Table 1.
- The results suggest a lower quality methodology in the Rare Diseases group, characterized by a higher number of single-arm studies, smaller sample sizes, and more frequent use of a biological endpoints.

TABLE 1. Clinical study methodology

Parameter	Statistical difference	Results
Study design	✓	**Non-comparative studies more frequent in Rare diseases group (Rare diseases : 22% vs. Others : 4% ; p = 0,0047)**
Study phase	✗	Majority of phase III studies in both groups (75% vs. 79% ; p = 0.2606)
Comparator	✓	**Active comparator less frequent in Rare Diseases group (24% vs. 46% ; p = 0.0014)**
Sample size	✓	**Smaller average sample size in Rare Diseases group (201.4 vs. 2,504.9 ; p = 0.0313).**
Primary endpoint	✓	**Biological primary endpoint more frequent in Rare diseases group (30% vs. 10% ; p = 0.0009)**
Significance of primary endpoint	✓	**Significant difference demonstrated less frequently in Rare Diseases group (76% vs. 90% ; p = 0.0019)**
Quality of life assessment	✗	Quality of life assessment conducted in most clinical studies in both groups (75% vs. 63% ; p = 0.2412)
Indirect comparaisons	✗	Use of at least one indirect comparison comparable between the two groups (16% vs. 20% ; p = 0.5623)

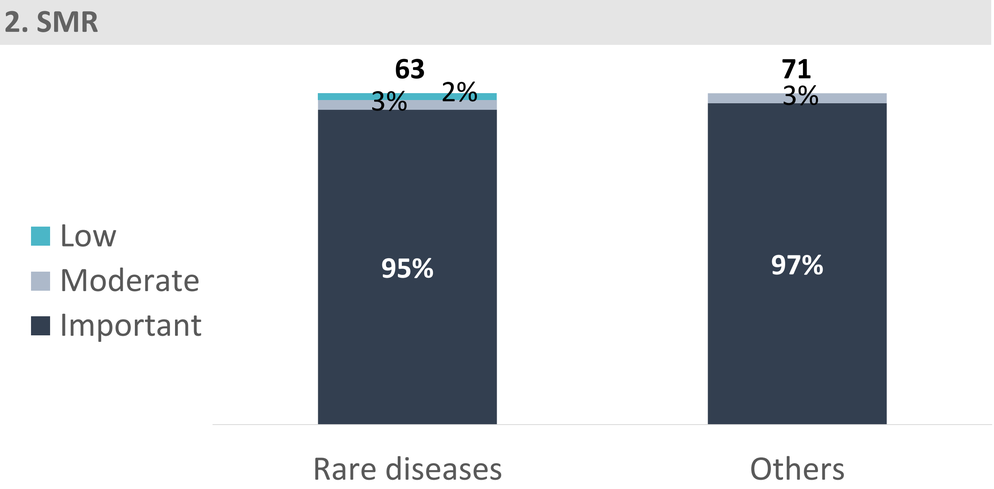
Quality of the clinical demonstration was more frequently criticized by the TC in the Rare diseases group:

- more frequent criticism of the primary endpoint (21% vs. 4% ; p=0,0086);
- criticism of the conduct of a single-arm study when a comparative study was deemed possible (9 evaluations in total, including 8 in Rare diseases group);
- benefit-risk ratio (B/R) considered poorly established in 3 evaluations in total, all within the Rare diseases group.

B. Results of the TC evaluation

- The mean time (SD) between marketing authorization (MA) and publication of the TC opinion was comparable between the two groups (Rare diseases: 226 (242) days vs. Others: 228 (297) days ; p = 0.9736).
- No statistically significant difference in SMR levels between the two groups, with a large majority of important SMR in both groups (Rare diseases: 95% vs. Others: 97% ; p = 0.7994). (Figure 2)

FIGURE 2. SMR



- No statistically significant difference in ASMR levels between the two groups, with ASMR IV most common in both groups (Rare diseases: 60% vs. Others: 52% ; p =0.321).
- Within the Rare diseases group a significant positive impact of the orphan status on the ASMR rating was demonstrated (p = 0.0111): no ASMR II for drugs without orphan status, compared to 8% for those with orphan status, and nearly three times more ASMR III for drugs with orphan status (46% vs. 17%).

FIGURE 3. ASMR

CONCLUSION

The primary challenge in rare diseases is designing clinical studies that provide robust evidence of the B/R ratio. Despite this difficulty, rare diseases appear to be assessed by the TC similarly to more common diseases, with comparable SMR and ASMR ratings. Consequently, the rarity of a disease does not directly affect the TC evaluation, particularly in recognizing an ASMR and its level.

1. *Orphanet. About rare diseases. Available at: https://www.orpha.net/fr/other-information/about-rare-diseases*
2. *Ministry of Labour, Health and Solidarity. Rare diseases. Available at: https://sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/article/les-maladies-rares*
3. *French Ministry of Solidarity and Health, French Ministry of Higher Education, Research and Innovation, Rare diseases health networks. National plan for rare diseases 2018-2022 (PNMR3).*
4. *A database designed to provide France with a homogeneous collection of clinical data, based on a minimum data set, to document the characteristics of patients with rare diseases, their management and care pathways in the French expert network.*

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