

CONTEXT

In Europe, a disease is considered rare if it affects fewer than one in 2,000 people¹. To date, nearly 7,000 rare diseases have been identified, impacting over 3 million patients in France². Access to medicines can be particularly challenging for these patients, with only 5% of rare diseases having a specific treatment approved³. As a result, rare diseases pose a major public health challenge, with a pressing need for effective therapies.

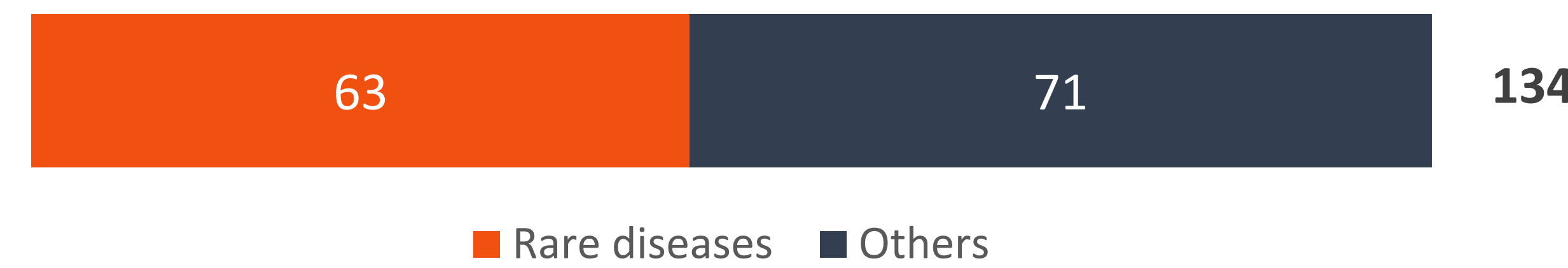
OBJECTIVE

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

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 comparisons	✗	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.

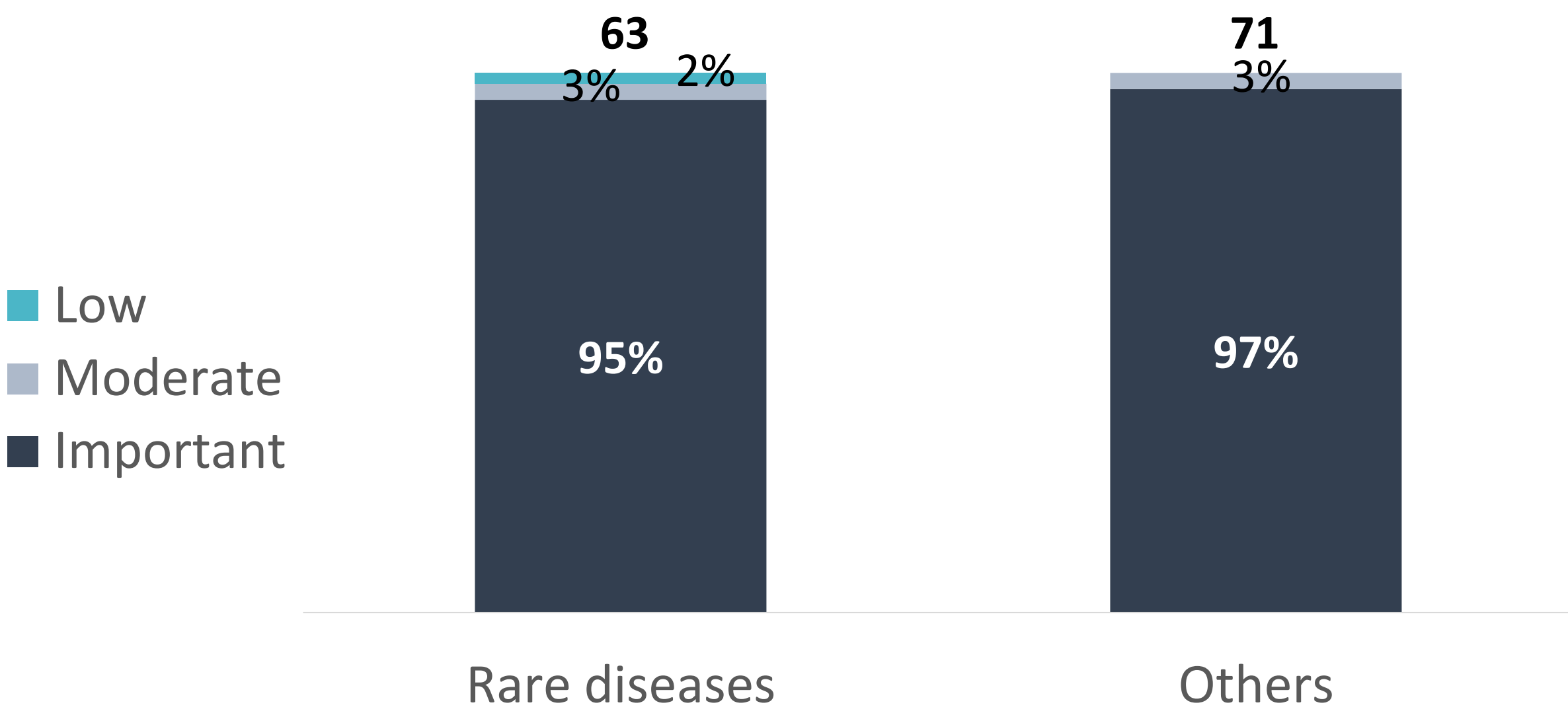
METHOD

- 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.

B. Results of the TC evaluation

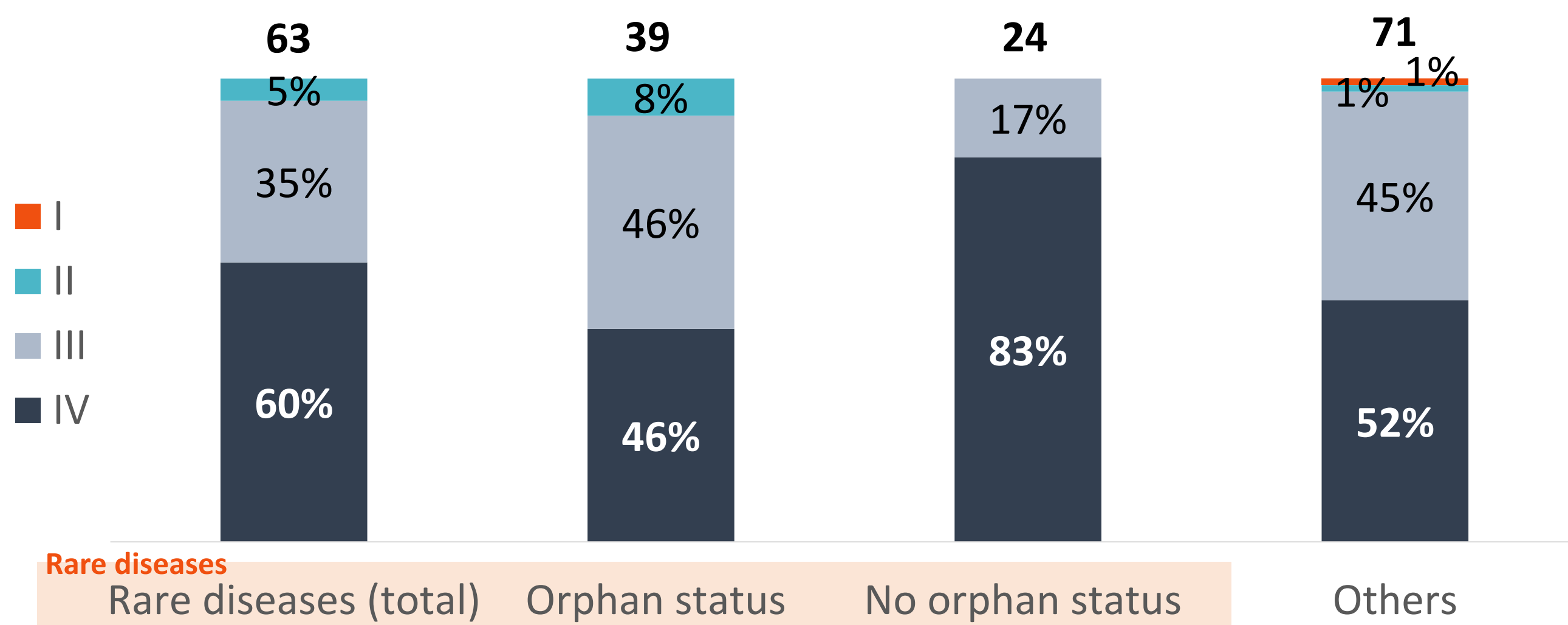
- The mean time (SD) between marketing authorization (MA) and publication of the TC opinion was comparable between the two groups (Rare diseases: 226 (242) days vs. Others: 228 (297) days ; p = 0.9736).
- No statistically significant difference in SMR levels between the two groups, with a large majority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

