HPR 209

EXPLORARE 2.0 Pivotal Studies for Rare Diseases: Will They Better Support Market Access?

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Background & Objectives

High prices requests and limited clinical evidence at market launch are considered barriers to the assessment, appraisal and market access of drugs for rare indications. The second edition of the EXPLORARE Project aimed to (i) analyze the pivotal studies of drugs/indications for rare diseases that are expected to be reimbursed by 2026 (ii) prioritize the actions suggested in the first edition, based on the opinion of experts in access (institutions, companies, patient associations and researchers).

Materials & Methods

Rare indications, expected to be appraised for the price and reimbursement status in Italy by 2026, and the relevant pivotal studies were retrieved from the Biomedtracker Database, US and European Clinical Trial Databases and Datamonitor Reports [1-4]. For clinical trials, the study design (RCT/Single-arm; for RCTs, Double-blind/Open-label) the presence of an active comparator or placebo, the type of primary endpoints, and the presence of Patient-Reported-Outcome-Measures (PROMs), among secondary endpoints, were analysed. The opinion of 78 Italian experts (HTA authorities, payers, industry, patient representatives) was gathered through a structured and validated questionnaire.

Results

We identified 154 new rare indications (Figure 1). Haematology, onco-haematology and oncology represent 21%, 18% and 16% of the sample, respectively. 77% of indications have orphan designation and 8% are ultra-rare drugs. More than 80% of pivotal trials are Phase III studies and single-arm accounts for only 36% of the trials. Almost 50% of RCTs are designed using an active comparator for control arms and 61% are double-blinded. Surrogate endpoints predominate among primary endpoints (82%) (Figure 2). 59% of studies include PROMs among secondary endpoints.

Figure 1 • Design of the studies analyzed (n=154)

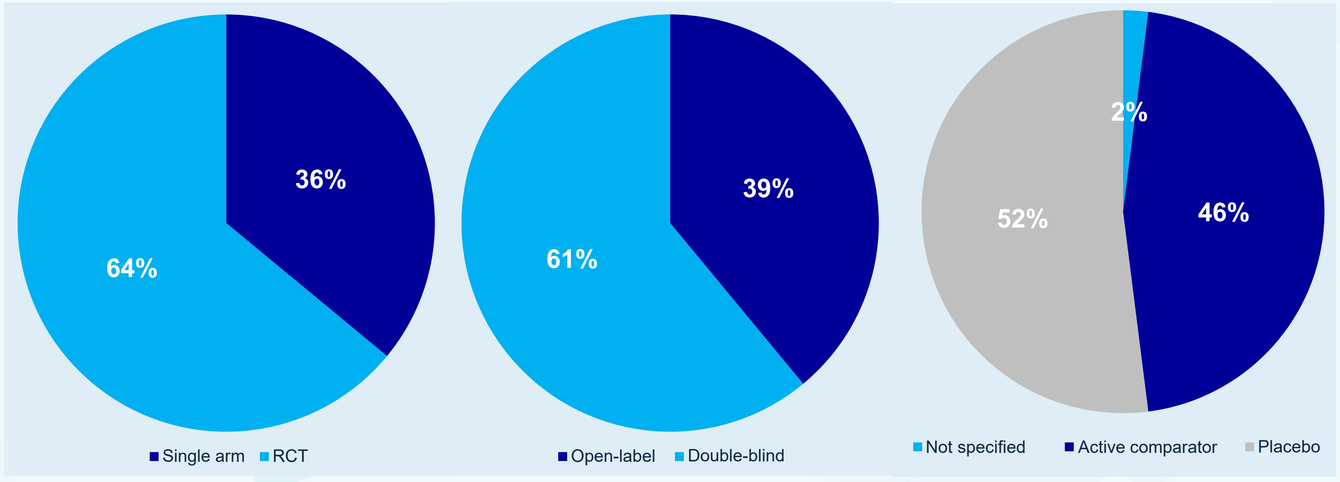
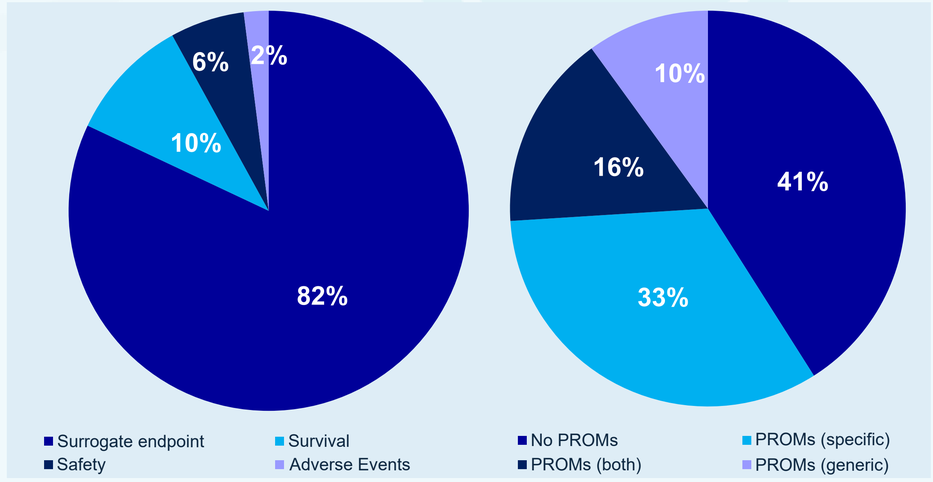


Figure 2 • Endpoints in clinical studies (primary endpoints & PROM's)



The response rate to the survey was 33% (26/78). Experts highlighted the importance of a more structured criteria to identify alternative treatments, a selective use of outcome-based managed entry agreements, and a structured early dialogue between the industry and AIFA (Italian Medicines Agency) to discuss uncertainties on the available evidence (Figure 3-5).

Figure 3 • Mean score given to actions aimed at simplifying and enhancing reproducibility of drug evaluations for rare diseases (1=most important / 6=least important)

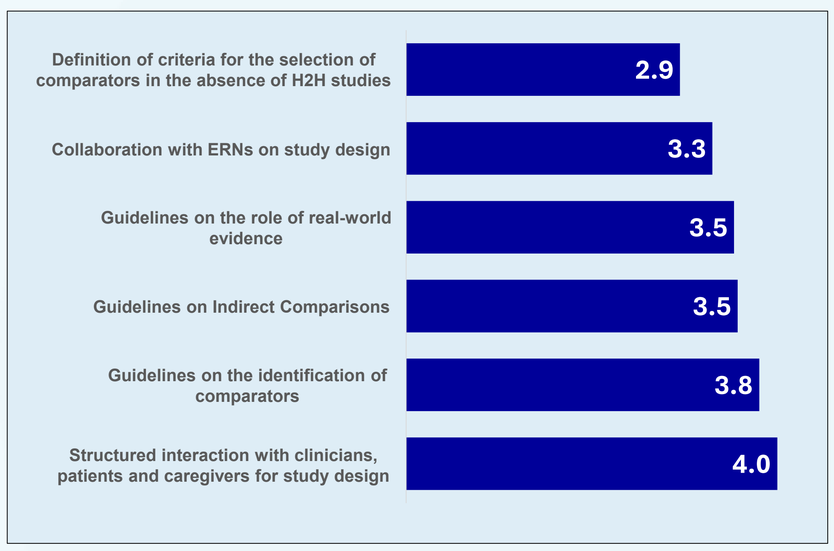


Figure 4 • Mean score given to tools that help reaching an agreement on price and reimbursement (1=most important / 5=least important)

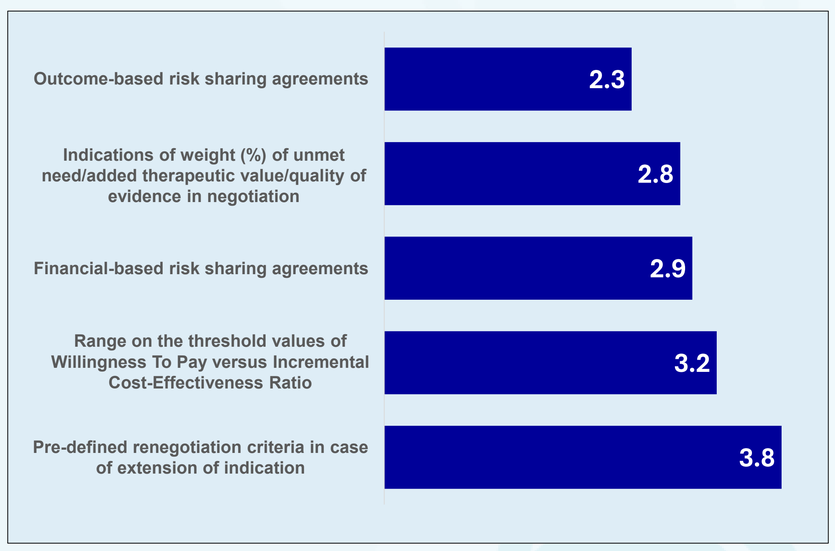
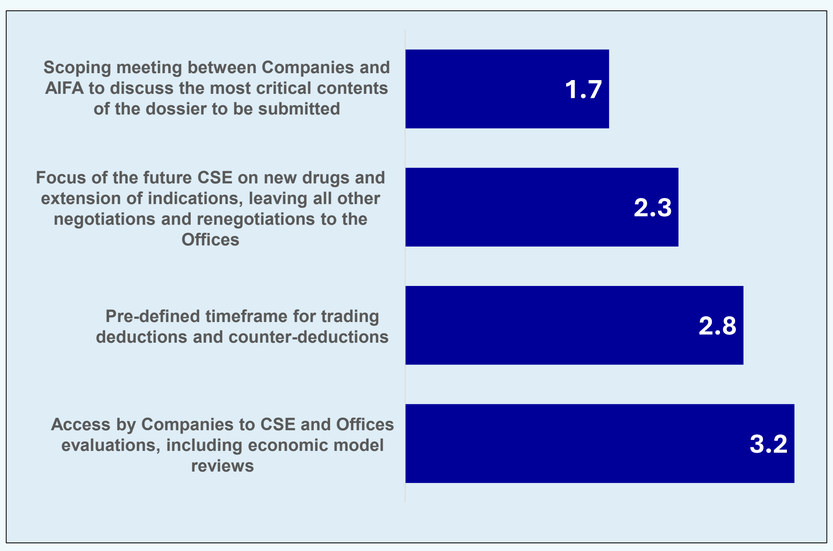


Figure 5 • Mean score given to interventions on the negotiation process with AIFA (1=most important / 4=least important)



Conclusions

Our findings were partially expected (extensive use of surrogate endpoints) and partially not (many RCTs with an active comparator in control arms). Having more head-to-head studies may reduce the uncertainty on evidence at market launch, but different issues persist, including the still limited role of PROMs and the quality of the pivotal studies, which was not investigated. Hence, despite the evidence on drugs for rare diseases has been strengthening, experts suggestions are still valid.

References

1. Biomedtracker Citeline (https://www.biomedtracker.com/, accessed Apr 2024). 2. Clincaltrials.gov (https://clinicaltrials.gov/, Accessed Apr 2024). 3. EU Clinical Trials Register. (https://www.clinicaltrialsregister.eu, Accessed Apr 2024). 4. EMA. The centralised procedure at EMA. (https://www.ema.europa.eu/, Accessed: Apr 2024).