Developing an Evidence Generation Plan for the Value Story of an Orphan Drug

PRO123

Schuurman S,[1] Siak S,[2] Taveau C,[3] Sidhu M[4]

[1]ICON plc, Stockholm, Sweden; [2]ICON plc, London, LON, UK; [3]ICON plc, Nanterre, France; [4]ICON plc, New York City, NY, USA

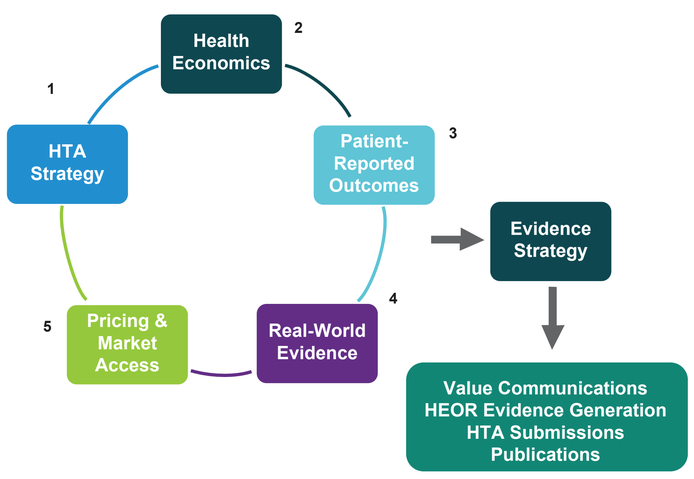
Background and Objectives

- Generating evidence for health technology assessment (HTA) submissions for an orphan drug can be challenging.
- Hurdles may include limited clinical trial data, lack of comparators, established endpoints or outcome measures, and absence of validated disease-specific quality-of-life (QoL) tools.
- In this study, we established an evidence generation plan (EGP) for a drug under development for a rare congenital disorder for the purpose of informing its value story and preparing for the future.

Methods

- To develop the EGP, we performed four tasks:
  1. Published European HTA reports (in the United Kingdom [including Wales], Germany, Norway, France and Sweden) of the drugs currently holding marketing authorization in the disease area and analogue disease area were evaluated.
     - Extracted information included the description of the document, treatment, patient population, manufacturer submission (both clinical and economic data), HTA committee assessments and decisions, other (eg, patient access scheme, pricing information, specialized technology assessments, other important information)
  2. HTA considerations identified in the first step were used to develop a discussion guide for an expert panel.
     - During the two-hour expert panel discussion, insights were obtained with regard to HTA strategy, health economics (HE), patient-reported outcomes (PRO), real-world evidence (RWE) and pricing and market access **(Figure 1)**.
  3. EGP actions were identified and classified according to priority for the launch of an orphan drug
     - High = key steps
     - Middle = steps to be taken after the key priorities
     - Low = optional steps
  4. We provided recommendations on the EGP strategy based on currently available data and the current market landscape.

Figure 1. Expert Panel Discussion: The Five Fields Informing the Strategy for Evidence Generation



HTA, health technology assessment; HEOR, health economics and outcomes research.

Results

- A total of eight documents were reviewed in the HTA landscape assessment.
- HTA considerations identified from the orphan drug submissions were grouped according to **(Figure 2)**:
  - Population
  - Comparator
  - Clinical outcomes
  - Cost-effectiveness outcomes
  - HTA appraisal routes
- During the expert panel discussion, several areas were identified as being critical for successful evidence generation in support of an orphan drug launch **(Figure 3).** Of these, three were considered high priority:
  - PRO instruments
  - Early economic modeling
  - Value proposition
- In addition, a recommendation was made to test these items via early scientific advice with the European Medicines Agency (EMA) and HTA agencies.
- A key take-away from our review and assessment of HTA submissions was the frequent criticism around uncertain QoL outcomes and the absence of validated disease-specific QoL instruments.
  - Addressing this issue, the expert panel recommended that PRO data be collected with a validated tool for the specific patient population.
- No tasks were identified as low priority.

Figure 2. Considerations Identified from the Review of Orphan Drug HTA Submissions

Population	• Generally no criticism of the target population as long as appropriate
Comparator	• Only when conventional therapy is not available, placebo is considered appropriate • Single-arm studies can be seen as a methodological limitation
Clinical Outcomes	• Uncertainty in QoL outcomes stemming from unvalidated disease-specific instrument should be considered • QoL data not obtained from patients but from proxies, such as caregivers, can be a reason for criticism • Limited or missing long-term efficacy and safety data can be a hurdle
Cost-Effectiveness Outcomes	• A cost-effectiveness analyses based on uncertain data arising from methodological issues in the underlying clinical trials is considered questionable • Use of appropriate/accepted endpoints in CE models is advised • Transparency of model and appropriate levels of complexity are considered appropriate
HTA Appraisal Routes	• There is no established process for ultra-orphan diseases across Europe • In the UK, the treatments are assessed through the Highly Specialised Technology appraisal route

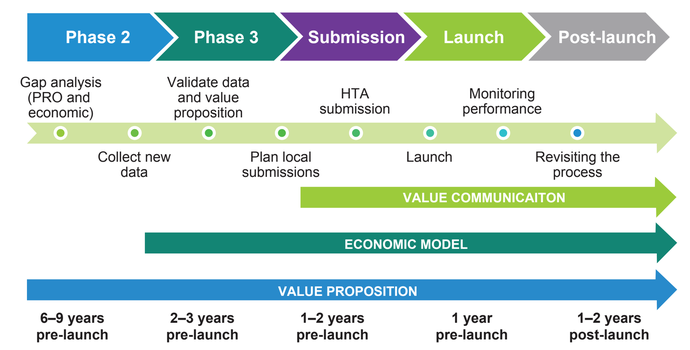
CE, cost-effectiveness; HTA, health technology assessment; QoL, quality-of-life.

Figure 3. Areas Identified as Critical for Evidence Generation in Support of an Orphan Drug Value Story

Patient-Reported Outcome Instruments	High	• Develop a conceptual PRO model to identify tools relevant to the specific patient population • Develop a strategy to fill identified gaps (eg, develop a new tool, validate an existing tool)
Early Economic Modeling	High	• Develop an early economic model to identify evidence gaps that will be required for a dynamic and robust model • Develop a strategy to gather additional data (targeted literature review, systematic literature review, network meta-analysis)
Value Proposition	High	• Develop an aspirational value proposition that includes messaging around added benefit, cost savings, and safety compared to a competitor or standard of care • Validate evidence with data from clinical trials and additional studies
Early Scientific Advice	Medium	• Seek EMA and/or HTA advice via Parallel Consultation or Multi-HTA Early Dialogue to inform the phase III trial and EGP
Utilize PRO Data	Medium	• Map PRO data to utilities to inform the economic model • PRO publication planning should be considered early and executed throughout the lifecycle of the asset
Real-World Evidence	Medium	• Conduct a feasibility assessment for the collection of RWE by mapping available databases • Observational studies (ie, trial follow-up) can collect additional data needed to develop the natural history of the disease
Pricing and Market Access	Medium	• Value message testing for physicians and payers (ie, pricing) • Archetype study with payers to determine priorities

EGP, evidence generation plan; EMA, European Medicines Agency; HTA, health technology assessment; PRO, patient-reported outcomes; RWE, real-world evidence.

Figure 4. Proposed Timeline for Evidence Generation in Support of an Orphan Drug Value Story



HTA, health technology assessment; PRO, patient-reported outcomes.

Discussion

- Evidence generation in orphan diseases can be challenging.
- By their very nature as rare diseases, orphan diseases do not lend themselves easily to evidence generation as they are associated with limited clinical trial data and a lack of comparators, established outcome measures and validated disease-specific QoL tools.
- Using a systematic approach that included an HTA landscape assessment and the gathering of expert insights, we developed an EGP and made recommendations on EGP strategy for an orphan drug.
- Among our key findings was that validated disease-specific PRO instruments, early economic modeling, and a value proposition were seen as the most important areas for evidence generation in support of a value story for an orphan drug.

Conclusion

- A well-established EGP is critical for overcoming payer uncertainty and facilitating a successful launch of an orphan drug treatment in Europe.
- Learnings from previous HTA assessments in the disease area and validation of the EGP by experts are important first steps in developing a value story in support of an orphan drug.

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