Payers may be concerned about the potential for the target population to expand to higher prevalence levels, with increasing

By taking a proactive and thoughtful approach to building the evidence dossier for an orphan drug, it should be possible to

Would patient interviews or vignettes demonstrate the relevance of the surrogate endpoint?

There are places where all these types of evidence can fall short, especially in the case of orphan diseases, where literature

Prospective observational studies of patients with less severe phenotypes may help to establish the disease burden and better

It is critical to reinforce the commitment to appropriate use.

Table 1. Key Questions Addressed in Early Scientific Advice … and How They Relate to Orphan Drugs

<table>
<thead>
<tr>
<th>Comparator/Standard of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>The standard of care in this disease is “watch and wait,” and I am not convinced that patients need a more aggressive treatment approach.</td>
</tr>
<tr>
<td>For many rare diseases, standard of care has been defined by the lack of suitable treatment options, leading to the perception that patients do reasonably well without active treatment. It is necessary to establish the true clinical burden and unmet need, including consequences of untreated disease progression, in the rare disease.</td>
</tr>
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<td>The pivotal trial should be designed to capture outcomes that are meaningful from a clinical, humanistic, and economic point of view.</td>
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  - Can real-world evidence correlate the trial’s primary endpoint with some more meaningful outcomes?
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You are showing me efficacy based on an endpoint that I can’t correlate to real life. Does this endpoint translate to

The economic analysis is not sufficiently robust: the inputs of the model rely on assumptions that are inadequately documented or supported. The planned but not powered?

Are the planned subgroup analyses sufficient for payers? Which must be powered, and which subgroup analyses should be

Keep the message focused on efficacy benefits in a disease characterized by substantial burden and unmet need.

It is essential to be upfront and clear about appropriateness of the trial design for an orphan drug.

An indirect treatment comparison may be useful in lieu of a head-to-head clinical trial, but this depends on the availability, quality, and relevance of published trials of other treatments.

A careful and comprehensive review of the literature may provide sufficient evidence on disease progression.

Disease simulation models can also be useful tools to correlate disease pathology with long-term clinical consequences.

A detailed chart review or other type of real-world study can reveal the true clinical burden and unmet need in a rare disease.

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