Are HTA agencies willing to accept single-arm trials as the main source of clinical evidence for the assessment of pediatric orphan drugs when faced with extenuating ethical and medical circumstances?

Barchanska, M[1]; Shaw, C[2]; Campbell, J[2]; Perez-Kempner, L[3]

1. Parexel International, Cracow, Poland; 2. Parexel International, London, UK; 3. Parexel International S.L., Madrid, Spain

Background

- The number of marketing authorizations for pediatric orphan drugs (PODs) has increased in recent years, many of which have been based on data from single-arm trials. These trials do not allow the direct assessment of the magnitude of added benefit compared with the SoC. This study aims to explore HTA agencies willingness to provide access to PODs with evidence based on single arm trials.

Methods

- PODs approved by the EMA between 2006-2022 were identified by screening the European Public Assessment Reports (EPAR) database.[1] PODs approved based solely on data from a single-arm trial were selected and the corresponding HTA reports were retrieved from four HTA agencies (i.e., NICE, HAS, CADTH, and TLV).

Results

- A total of 19 PODs were approved by the EMA, of which four were approved based solely on data from single-arm trials. Nine corresponding HTA submissions were retrieved (four from NICE, two from HAS, and two from CADTH). Overall, all PODs evaluated received a positive recommendation for reimbursement by HTA agencies, five of which were restricted to specific conditions (**Table 1**). All submissions included manufacturers´ justification for the single-arm trial design (**Figure 1**). In the absence of trial comparators, all submissions included either an MAIC versus standard of care or naïve comparison versus natural history cohort to demonstrate the comparative value (**Figure 2**). Three MAICs (60%) were not accepted by HTA agencies due to methodological weaknesses (e.g., significant heterogeneity between studies) that severely limited the results. In all nine submissions the lack of direct comparative evidence versus the standard of care was criticized by HTA agencies but was not perceived as a critical barrier to access due to high disease burden in a given population, lack of treatment alternatives, patient's poor prognosis, curative potential of the therapy, or innovativeness of the product.

Table 1: HTA appraisal outcomes

	Tisagenlecleucel	Onasemnogene abeparvovec	Atidarsagene autotemcel	Selumetinib
	R/R B-ALL in people ≤ 25 years	SMA in patients < 2 years	MLD in children	Symptomatic and inoperable PN in children ≥ 3 years
NICE (England)	• Managed access agreement • Restricted to use within the CDF[2]	• Patient access scheme • Restricted to subpopulation[3]	• Patient access scheme / commercial agreement[4]	• Patient access scheme / commercial agreement[5]
HAS (France)	• SMR: Important / ASMR: III (moderate)[6]	• SMR: Important / ASMR: III (moderate)[7]	• SMR: Important / ASMR: III (moderate) • Restricted to subpopulation[8]	• *No assessment available*
CADTH (Canada)	• Recommendation under the condition of price reduction[9]	• Recommendation under the condition of price reduction • Restricted to subpopulation[10]	• *No assessment available*	• *No assessment available*

Positive recommendation | Recommendation with restriction

Figure 1: Manufacturers' rationale for the single-arm trial design

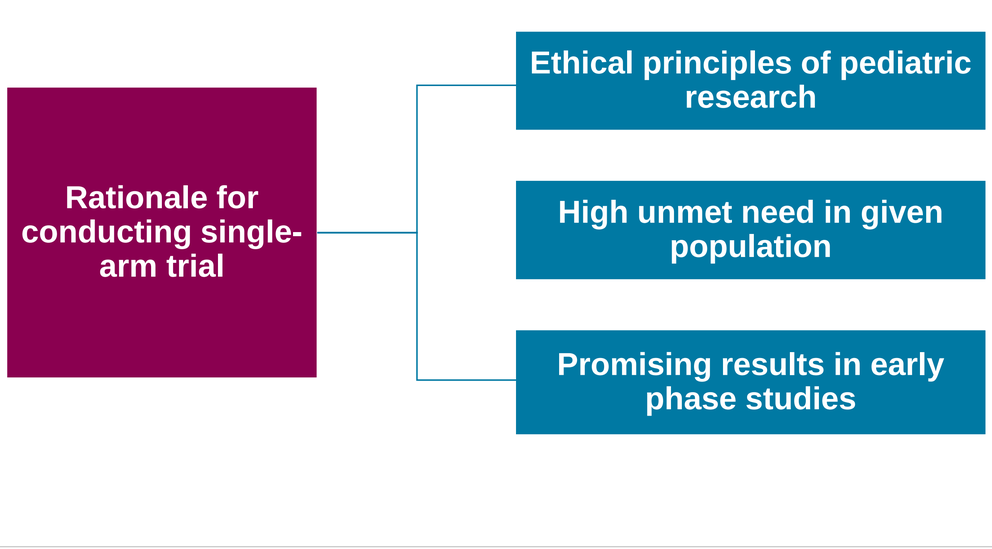
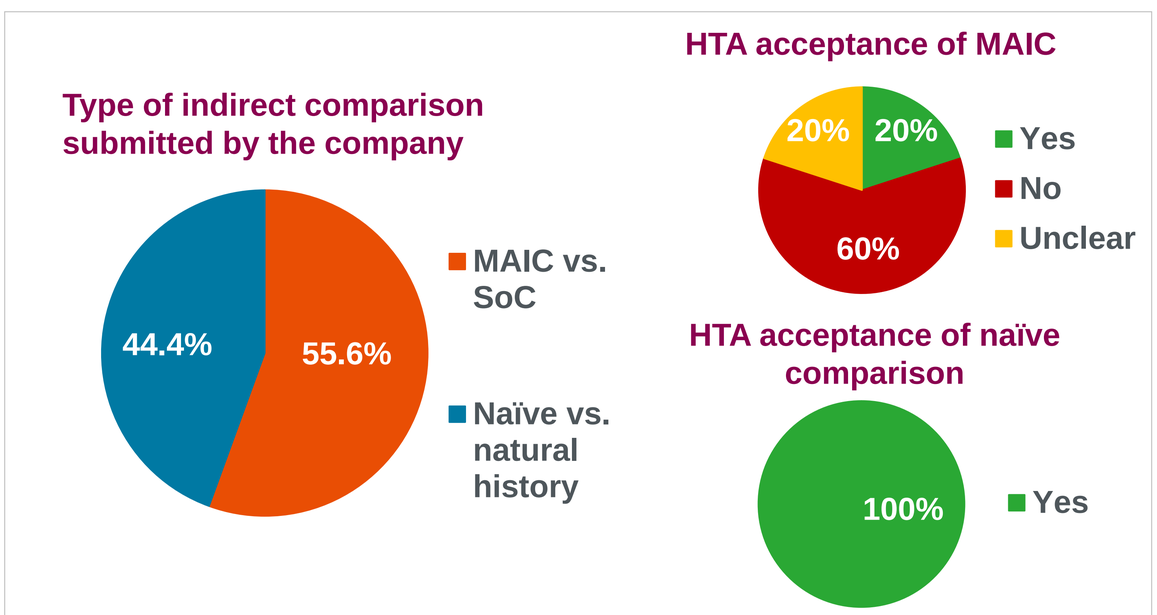


Figure 2: Type and acceptance of indirect comparison submitted



Conclusions

- Single-arm trials for PODs can be accepted as a source of clinical evidence under extenuating ethical and medical circumstances (i.e., high unmet need, significant disease burden). In the absence of RCTs, manufacturers must provide justification for the trial design and the potential benefit (i.e., promising results in early phase trials) and identify alternative strategies to demonstrate the magnitude of added benefit versus standard of care. Early payer and scientific engagement can help define the perceived level of unmet need and likelihood of reimbursement based on clinical evidence with varying levels of robustness.

ASMR: Clinical added value; B-ALL: B-cell acute lymphoblastic leukemia; CADTH: Canadian Agency for Drugs and Technologies in Health; CDF: Cancer Drug Fund; EMA: European Medicines Agency; EPAR: European public assessment report; HAS: French National Authority for Health; HTA: Health technology assessment; ITC: Indirect treatment comparison; MAIC: Matched indirect treatment comparison; MLD: Metachromatic leukodystrophy; NICE: National Institute for Health and Care Excellence; PN: Plexiform neurofibromas; POD: Pediatric orphan drug; R/R: relapsed/refractory; SoC: Standard of care; SMA: Spinal muscular atrophy; SMR: Actual benefit; TLV: Swedish Dental and Pharmaceutical Benefits Agency

1. https://www.ema.europa.eu/sites/default/files/Medicines_output_european_public_assessment_reports.xlsx **2.** www.nice.org.uk/guidance/ta554. **3.** www.nice.org.uk/guidance/hst15. **4.** www.nice.org.uk/guidance/hst18. **5.** www.nice.org.uk/guidance/hst20. **6.** www.has-sante.fr/jcms/p_3262256. **7.** www.has-sante.fr/jcms/p_3225241. **8.** www.has-sante.fr/jcms/p_3263782. **9.** www.cadth.ca/sites/default/files/pdf/car-t/op0538-recommendations-report-jan2019.pdf. **10.** www.cadth.ca/onasemnogene-abeparvovec.