

Background		EMA feedback on ECA	
Product; indication	Main trial and ECA data source(s)	Limitations	Strengths
<b>Acceptable</b>			
Amvuttra (vutrisiran); amyloid polyneuropathies, familial	<ul style="list-style-type: none"> <li>Main: RCT with an active comparator arm (n = 122) but no "untreated" arm</li> <li>ECA: RCT data (n = 77)</li> </ul>	<ul style="list-style-type: none"> <li>Baseline differences between comparator groups were considered to limit the comparability of results.</li> </ul>	<ul style="list-style-type: none"> <li>ECA results were considered confirmatory for the efficacy of the drug.</li> <li>Both studies (main and ECA) were sponsored by the same company, and the ECA study was designed to be similar to the main.</li> </ul>
Zokinvy (lonafarnib); progeria, laminopathies	<ul style="list-style-type: none"> <li>Main: 2 SATs with no control arm (n = 27, 35)</li> <li>ECA: Registry data (n = 81)</li> </ul>	<ul style="list-style-type: none"> <li>Matching on all important prognostic factors was not performed due to lack of data in the ECA, but the approach used was considered the best possible.</li> <li>The choice of an external comparator is justified and may "exceptionally support efficacy" but does not ensure group comparability and is associated with many uncertainties.</li> <li>Concerns about bias and confounding were noted due to the inherent differences between clinical trial and real-world patients' demographics, clinical characteristics and healthcare received.</li> </ul>	<ul style="list-style-type: none"> <li>The ECA is acceptable given the existence of a single register for the disease including all known patients.</li> <li>Immortal time bias is not a reason for concern in this study (disease starts at birth, alignment of time 0 is easier).</li> <li>Despite the potential for confounding and bias in ECAs, results are considered confirmatory of the efficacy effect given the sufficiently large, estimated effect and the number of sensitivity analyses.</li> </ul>

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<b>Supportive</b>			
Agamree (vamorolone); muscular dystrophy, Duchenne muscular dystrophy	<ul style="list-style-type: none"> <li>▪ Main: RCT with an active comparator arm (n = 121); ECA used for comparison against another active treatment</li> <li>▪ ECA: RCT data (n = 196)</li> </ul>	<ul style="list-style-type: none"> <li>▪ There were concerns that the selection of control patients introduced selection bias given the limited availability of data.</li> <li>▪ Lack of some key baseline covariates limited interpretation of the comparison.</li> <li>▪ ECA results indicated that the treatment had inferior efficacy to comparators; however, ECA evidence needs to be interpreted cautiously, is of limited value, and confirmation of the efficacy cannot be concluded for methodological reasons.</li> </ul>	<ul style="list-style-type: none"> <li>▪ The ECA results were deemed generally acceptable, given the limitations to find long-term controls for the treatment arm.</li> </ul>
Breyanzi (lisocabtagene maraleucel); lymphoma, large B-cell, diffuse	<ul style="list-style-type: none"> <li>▪ Main: 2 SATs (n &gt; 300)</li> <li>▪ ECA: Aggregated data from SLR (n = 45 studies), and individual patient data from a retrospective medical records study (n = 407)</li> </ul>	<ul style="list-style-type: none"> <li>▪ It is noted that the inability to control bias restricts the use of ECAs to where the treatment effect is dramatic and the usual course of the disease highly predictable.</li> <li>▪ Given the significant clinical and biological heterogeneity of the disease under study, results from the ECAs can only be accepted to contextualise results, but their contributions to inform benefit-risk evaluations is limited.</li> </ul>	None
Carvykti (ciltacabtagene autoleucel); multiple myeloma	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 97)</li> <li>▪ ECA: Data from retrospective chart review natural history study (n = 275)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Limitations of ECA methods described by the MAA are noted.</li> </ul>	<ul style="list-style-type: none"> <li>▪ The ECA study is considered to be supportive to contextualise the efficacy results, namely time to event endpoints.</li> </ul>

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Ebvallo (tabelecleucel); lymphoproliferative disorders	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 27)</li> <li>▪ ECA: Data from an EHR's database (n = 84)</li> </ul>	None discussed.	<ul style="list-style-type: none"> <li>▪ Despite well-known limitations of ECAs, ECA data were considered supportive for contextualisation of efficacy results.</li> <li>▪ The ECA results showed a significant benefit of treatment compared with standard of care and are consistent with the pivotal study results.</li> </ul>
Elrexio (elranatamab); multiple myeloma	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 123)</li> <li>▪ ECA: Data from 2 databases of EHRs (n = 152, 233)</li> </ul>	<ul style="list-style-type: none"> <li>▪ A key limitation noted is that the study period does not include the time when state-of-the-art therapies were available.</li> <li>▪ Other limitations of the RWD are the lack of consistent monitoring and application of disease evaluation criteria, along with unmeasured confounding.</li> </ul>	<ul style="list-style-type: none"> <li>▪ It is agreed that the compared populations are broadly similar.</li> <li>▪ It is noted that the ECA analysis is conducted and reported in a satisfactory manner.</li> <li>▪ Although not replacing randomised comparisons, it is concluded that the ECA results contextualise the effect estimates and are supportive of the claimed indication.</li> </ul>
Jeraygo (aprocitentan); hypertension	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 730)</li> <li>▪ ECA: Data from an observational study (n = not reported) and aggregate data from SLR (n = not reported)</li> </ul>	<ul style="list-style-type: none"> <li>▪ EMA noted that although ECA evidence is supportive and can contextualise the safety evaluation, it does not serve as substitute for controlled data to characterise cardiovascular safety.</li> <li>▪ The ECA evidence was considered insufficient to provide reassurance on safety findings and it was not considered robust enough to enable reliable conclusions on the risk of major cardiovascular events in an already high-risk population.</li> </ul>	None

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Nulibry (fosdenopterin); metal metabolism, inborn errors	<ul style="list-style-type: none"> <li>Main: 3 SATs (n = 4, 8, 3)</li> <li>ECA: Data from 2 natural history cohorts: a prospective and a retrospective study (n = 37, 6)</li> </ul>	<ul style="list-style-type: none"> <li>Although the use of an ECA is considered justified in this case, it is noted that it "<i>inherently leads to bias</i>" and the quality of the [ECA] evidence is not sufficient to justify full approval, and it can only be seen as descriptive and supportive.</li> </ul>	<ul style="list-style-type: none"> <li>The rationale for the ECA was accepted as a placebo control and was unfeasible due to the rare nature and rapid progression of the disease without treatment options.</li> <li>Rationale for providing ECA evidence was justified as the natural history of the disease was predictable, the expected treatment effect large, and the endpoints' objective.</li> <li>Regional overlap between comparator groups was noted as a strength and selection bias was considered unlikely.</li> <li>Studying a treatment policy strategy was accepted, but there were concerns about ignoring intercurrent competing events (i.e., death).</li> </ul>
Scemblix (asciminib); leukemia, myelogenous, chronic, <i>BCR-ABL</i> positive	<ul style="list-style-type: none"> <li>Main: RCT with an active comparator arm (n = 157); ECA used for comparison against another active treatment</li> <li>ECA: RCT data (n = 203)</li> </ul>	<ul style="list-style-type: none"> <li>The main limitations noted were the low number of patients and the absence of preplanned efficacy assessments.</li> </ul>	<ul style="list-style-type: none"> <li>Mostly agreed that the populations [from main and ECA groups] were similar. The MAIC approach and matching criteria were preliminarily agreed upon, and the methods and results were satisfactorily described in detail.</li> </ul>

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Skyclarys (omaveloxolone); Friedreich ataxia	<ul style="list-style-type: none"> <li>Main: RCT with a single-arm OLE phase (n = 149)</li> <li>ECA: Data from medical registry (n = 136)</li> </ul>	<ul style="list-style-type: none"> <li>The selection of the eligible participants based on the availability of data raised concerns about selection bias.</li> </ul>	<ul style="list-style-type: none"> <li>PS matching on the specific list of covariates chosen for adjustment are considered suitable methods to support findings of the main trial, given the rarity of the disease and the high unmet clinical need.</li> <li>Validation of the control group by comparing it to the main trial's control group (pre-OLE phase) strengthened the ECA comparisons, as did the additional sensitivity analyses. ECA results have supported the overall efficacy conclusion.</li> </ul>
Upstaza (eladocagene exuparvovec); amino acid metabolism, inborn errors	<ul style="list-style-type: none"> <li>Main: SAT (n = 28)</li> <li>ECA: Data from published literature (n = 82 patients)</li> </ul>	<ul style="list-style-type: none"> <li>A key limitation is the lack of balance between comparator groups in terms of their age, genotype, and baseline scores.</li> <li>Control data taken from published literature, while useful to contextualise, is not considered robust enough for statistical comparison, particularly with a small sample size.</li> </ul>	<ul style="list-style-type: none"> <li>There was a significant treatment benefit of the product when compared with the ECA.</li> <li>Despite the limitations of the ECA, it was the best available data.</li> </ul>

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Xenpozyme (olipudase alfa); ASMD type A/B or type B	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 15)</li> <li>▪ ECA: Data from a prospective natural history study (n = 14)</li> </ul>	<ul style="list-style-type: none"> <li>▪ The standard deviation of the outcome measure is much larger in the ECA group than in the main trial group, indicating lower precision.</li> </ul>	<ul style="list-style-type: none"> <li>▪ ECA studies were deemed helpful to inform about the disease course in paediatric patients.</li> <li>▪ EMA noted that despite differences in outcome characterisation between main trial and external study, the evidence can be accepted.</li> <li>▪ Results from ECA study in the paediatric population showed clinical improvements consistent with the results from the RCT conducted in adults.</li> </ul>
Zilbrysq (zilucoplan); myasthenia gravis	<ul style="list-style-type: none"> <li>▪ Main: RCT with a single-arm OLE phase (n = 174)</li> <li>▪ ECA: Aggregated data from SLR (n = 6 studies with 312 patients). Individual data from a registry (n = 16) and an RCT (n = 53)</li> </ul>	<ul style="list-style-type: none"> <li>▪ While partly addressed by the sensitivity analyses performed, concerns about the potential for residual bias from unmeasured confounders or unmet model assumptions remain.</li> <li>▪ The ECA evidence is considered inferior to an RCT.</li> </ul>	<ul style="list-style-type: none"> <li>▪ The strong effort to find appropriate comparable subjects with similar disease and patient characteristics was valued.</li> <li>▪ The efforts for transparency and detailed description of the statistical methods and consideration of the multiple analytical options were valued.</li> <li>▪ Sensitivity analyses' results were consistent and considered to support the main results.</li> </ul>

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<b>Not supportive</b>			
Albrioza (sodium phenylbutyrate/ ursodoxicoltaurine); amyotrophic lateral sclerosis	<ul style="list-style-type: none"> <li>▪ Main: RCT with a single-arm OLE phase (n = 137)</li> <li>▪ ECA: Data from a registry (n = unk) and from a clinical trial's database (n = unk)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Post hoc analyses with insufficient details provided on methodology.</li> <li>▪ The value of ECA was of limited importance and was not considered to add any valuable information to the main trial.</li> <li>▪ The lack of methodological details and post hoc decisions on the ECA comparisons were of concern.</li> </ul>	None
Columvi (glofitamab); lymphoma, large B-cell, diffuse	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 108)</li> <li>▪ ECA: Aggregated data from previous RCTs (n = not reported)</li> </ul>	<ul style="list-style-type: none"> <li>▪ The indirect comparison used for the ECA was not deemed useful for benefit-risk assessment.</li> </ul>	None
Livmarli (Maralixibat chloride); Alagille syndrome	<ul style="list-style-type: none"> <li>▪ Main: RCT of drug withdrawal (n = 84). ECA needed to compare effects against a treatment naïve arm.</li> <li>▪ ECA: Registry data (n = 490)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Comparisons against ECA are considered problematic and susceptible to selection bias.</li> <li>▪ Relevant uncertainties in the methodology limited the value of the ECA.</li> <li>▪ Baseline differences between comparator groups inherent in the fact that one was clinical data and the other RWD were considered to limit the comparability of results.</li> <li>▪ Potential residual confounding, informative censoring, and differential drop-out.</li> </ul>	None

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Omblastys (iodine-131 omburtamab); neuroblastoma	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 107)</li> <li>▪ ECA: Registry data (n = 112)</li> </ul>	<ul style="list-style-type: none"> <li>▪ The EMA noted the following concerns about the ECA evidence: <ul style="list-style-type: none"> <li>– Unknown and unquantifiable bias</li> <li>– Baseline differences between comparator groups</li> <li>– Known prognostic factors not included in the analysis.</li> <li>– Small effect size in a context with potential residual confounding</li> <li>– Differences in data quality</li> <li>– Post hoc decisions and data-driven choices about which variables to include in the PS model</li> <li>– Residual bias makes ECA results not comparable to the standard from a RCT.</li> </ul> </li> </ul>	None
Tabrecta (capmatinib); carcinoma, non-small cell lung cancer	<ul style="list-style-type: none"> <li>▪ Main: SAT (n = 373)</li> <li>▪ ECA: Data from 2 EHR's databases (n = 20, 41)</li> </ul>	<ul style="list-style-type: none"> <li>▪ The ECA evidence has several limitations that preclude its interpretation as comparative evidence: small sample size in the ECA cohort, not systematically conducted assessments of efficacy outcomes, treatment assignment based on post-baseline events, rapidly changing clinical treatment and diagnostic landscape of the disease during study period, use of study drug by 30% of control patients in the RWD during follow-up, and unmeasured confounding.</li> <li>▪ The methodological deficiencies make the ECA evidence "supportive at best."</li> </ul>	None

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Talvey (talquetamab); multiple myeloma	<ul style="list-style-type: none"> <li>Main: SAT (n = 143)</li> <li>ECA: Data from 2 prospective observational cohorts (n = 165)</li> </ul>	<ul style="list-style-type: none"> <li>The relevance of the ECA evidence for regulatory purposes is considered limited due to the intrinsic limitations of indirect comparisons, particularly in the context of disease with significant clinical, biological, and treatment-related heterogeneity.</li> </ul>	None
Tepkinly (epcoritamab); lymphoma, large B-cell, diffuse	<ul style="list-style-type: none"> <li>Main: SAT (n = 157)</li> <li>ECA: Data from EHR's databases (n = 573) and from an RCT (n = 154)</li> </ul>	<ul style="list-style-type: none"> <li>The differences between compared populations limited the interpretation of the analyses.</li> <li>The use of RWD was considered very uncertain.</li> </ul>	None
Sohonos (palovarotene); myositis ossificans	<ul style="list-style-type: none"> <li>Main: SAT (n = 107)</li> <li>ECA: Data from a prospective observational cohort (n = 114)</li> </ul>	<ul style="list-style-type: none"> <li>The ECA was a post hoc data-driven analysis that was not considered scientifically nor clinically justified.</li> <li>The study is biased due to methodological issues, such as considerable baseline differences between compared populations and primary endpoint assessments.</li> <li>The discrepancy of results between different analyses questions robustness of the findings.</li> </ul>	None

ASMD = acid sphingomyelinase deficiency; ECA = external control arm; EHR = electronic health record; EMA = European Medicines Agency; EPAR = European Public Assessment Report; MAA = marketing authorization applicant; MAIC = matching adjusted indirect comparison; OLE = open-label extension; PS = propensity score; RCT = randomised controlled trial; RWD = real-world data; SAP = statistical analysis plan; SAT = single-arm trial; SLR = systematic literature review.

Note: Study design features not described in EPARs may have been described in the study protocols, SAPs, and reports and not captured by this review.