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EVALUATION OF THERAPIES LAUNCHING WITHIN A SPACE WITH NO APPROVED STANDARD OF CARE

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INTRODUCTION

Therapies that launch in disease areas with no alternative treatment options represent a challenge in demonstrating value due to the lack of comparative evidence that prove an added therapeutic benefit.

Demonstrating the value of a therapy and presenting a strong case of efficacy and safety of a drug is inevitably more complicated for drugs that launch in a space with no approved standard of care (SoC). Health technology assessment (HTA) agencies typically require randomized controlled trial evidence when appraising health technologies. As a result, the lack of approved SoC and therefore lack of comparative clinical data necessary to support an HTA submission may be challenged by payers. These therapies often rely on surrogate endpoints that may not be validated (e.g., with evidence that demonstrates the link between treatment-induced change on surrogate endpoint and treatment-induced change on patient-relevant endpoint), and the use of such endpoints adds uncertainty to the HTA process. Additionally, payers may not be as knowledgeable about the disease and may not appreciate the burden for patients and the high unmet need. Consequently, HTA processes will always be more challenging for these therapies.

The purpose of this research was to explore HTA outcomes for therapies launching in disease areas with no approved standard of care and highlight key evidence strategies to address data gaps and optimize HTA outcomes.

OBJECTIVE

To identify optimal evidence development strategies for therapies with indications where there is no established SoC in Germany, France, and the UK.

METHODS

An initial list of all EMA-approved therapies was extracted from the EMA website and filtered to identify therapies approved between 2011 and 2020. A total of 97 orphan therapies were further selected, which were screened for mention of no alternative treatment options in the HTA decision summaries from G-BA in Germany, HAS in France and NICE in the UK. This identified 15 therapies to explore the trial design, efficacy outcomes and supplementary evidence (FIGURE 1). A final list of 4 key orphan therapies demonstrating differences across key metrics and evidence submitted were selected for deep dive to allow for extrapolation of findings. An additional analogue, XIAPEX, was included in the analysis to understand evidence requirements for therapies that, while not receiving an orphan designation by the EMA, launch in a space with no established SoC.

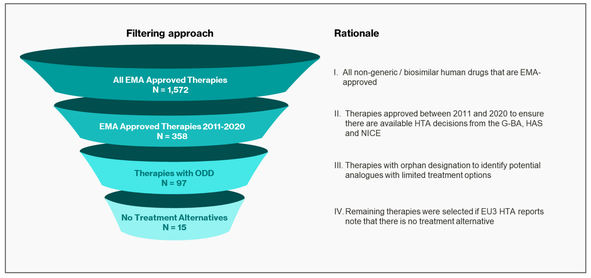

FIGURE 1: FILTERED APPROACH TO IDENTIFY RELEVANT THERAPIES THAT LAUNCH IN DISEASE AREAS WITH LIMITED TREATMENT OPTIONS

RESULTS

While a non-quantifiable added benefit rating was assigned to most studied therapies in Germany given the orphan status, French and UK HTA bodies were more stringent in their assessment of prioritized analogues, requesting more data to confirm the extent of the benefit (FIGURE 2).

Product	ROA	EMA Indication	HTA Outcomes DEU	HTA Outcomes FRA	HTA Outcomes GBR
Palynziq (pegvaliase-pqpz) Injection	SQ	Treatment of patients with **Phenylketonuria** (PKU) aged 16+ with inadequate blood phenylalanine control* despite prior treatment	NON-QUANTIFIABLE ADDED BENEFIT	SMR MODERATE; ASMR IV	*UNDER REVIEW*
LUXTURNA (voretigene neparvovec-rzyl)	Subretinal Injection	Adult and pediatric patients with **vision loss due to Inherited Retinal Disease** caused by confirmed **biallelic *RPE65* mutations**	CONSIDERABLE ADDED BENEFIT	SMR IMPORTANT; ASMR II	REIMBURSED W/ COMMERCIAL ARRANGEMENT
Strensiq (asfotase alfa)	IV	Long-term **enzyme replacement therapy** in patients with **pediatric-onset Hypophosphatasia**	NON-QUANTIFIABLE (infantile, ages <5). NO ADDED BENEFIT (juvenile, ages 5+)	SMR IMPORTANT; ASMR II	REIMBURSED W/ MANAGED ENTRY ARRANGEMENT
Kanuma (sebelipase alfa)	IV	**Long-term enzyme replacement therapy** in patients of **all ages** with **Lysosomal Acid Lipase Deficiency**	NON-QUANTIFIABLE ADDED BENEFIT	SMR IMPORTANT, ASMR III (ages < 2); SMR WEAK, ASMR V (ages 2+)	NOT REIMBURSED
XIAPEX (clostridium histolyticum)	IV	Treatment of **Dupuytren's Contracture** in adults with a **palpable cord**	NO ADDED BENEFIT	SMR INSUFFICIENT	*WITHDRAWN*

*Defined As Blood Phenylalanine Levels Greater Than 600um / L

Orphan Designation · Positive Outcome · Neutral Outcome · Negative Outcome

FIGURE 2: OVERVIEW OF HTA OUTCOMES FOR PRIORITIZED ANALOGUES IN GERMANY, FRANCE, AND THE UK

PALYNZIQ was approved using a biomarker endpoint that measures the change in patients' blood phenylalanine levels throughout the course of treatment (FIGURE 3).

The transparency committee (TC) in France was acceptant of this surrogate endpoint, expecting that improved biomarker levels will lead to long-term improvement in neurocognitive symptoms for patients that do reach recommended target levels of phenylalanine.

However, additional quality-of-life (QoL) endpoints to demonstrate this symptomatic improvement were not provided, potentially limiting PALYNZIQ's HTA opportunity in France.

In the UK, evaluation of PALYNZIQ is still ongoing as additional health economic and cost-effectiveness evidence to support the NICE appraisal are still under development.

Product	Trial Design	Comparator Acceptability DEU	Comparator Acceptability FRA	Comparator Acceptability GBR	Primary Endpoint	Endpoint Acceptability DEU	Endpoint Acceptability FRA	Endpoint Acceptability GBR	Efficacy Outcomes
Palynziq	Phase 3, 36-week RCT vs. Placebo; N=261	✓	✓	N/A	Reduction in blood phenylalanine levels	✓	✓	N/A	-879.7 umol / L (p < 0.0001) blood phenylalanine vs. placebo
LUXTURNA	Phase 3, 52-week RCT vs. Best Supportive Care (BSC); N=31	✓	✓	✓	Change in multi-luminance mobility testing (MLMT) score after 1 year	✓	✓	✓	+1.6 (p = 0.001) vs. Best Supportive Care (BSC)
Strensiq	Phase 1/2, 24-week Single-Arm Trial; N=11	✓	✓	✓	Change in rickets severity based on the assessment of skeletal radiographs using RGI-C	✓	✓	✓	+2 and +3 in RGI-C over 6 months of exposure
Kanuma	Phase 1/2, 20-week Single-Arm Trial; N=11	–	✓	✓	12-month survival rate	–	✓	✓	67%
XIAPEX	Phase 3, 90-day RCT vs. Placebo; N=306	×	×	N/A	% patients achieving a reduction of contracture to ≤5º 30 days after last injection	–	–	N/A	64% (ITT) vs. 6.8% (placebo)

Accepted · Neutral · Not Accepted

FIGURE 3: SUMMARY OF CLINICAL STUDY DESIGN AND PRIMARY EFFICACY OUTCOMES FOR EACH PRIORITIZED ANALOGUE

LUXTURNA was approved based on improvements in patient vision test scores after 1 year of treatment, and all EU3 countries viewed the use of this novel disease-specific endpoint as acceptable.

NICE however noted that, while the MLMT primary endpoint is acceptable to inform efficacy in the short term, more established vision outcomes (i.e., visual function or visual acuity) were the primary instruments used in health economic modeling.

Given the demonstrated improvement using accepted endpoints and favorable clinical efficacy, LUXTURNA received positive HTA ratings in France and Germany (ASMR II and considerable added benefit, respectively).

STRENSIQ was EMA-approved and received reimbursement across EU3 countries with single-arm trial data, a comparison to a historical control group, and retrospective analyses that assessed overall survival as well as symptom improvement (FIGURE 4).

Overall survival data and the indirect comparison using a historical control group were considered significant in France, leading to an ASMR II rating, but the G-BA did not accept STRENSIQ's non-comparative data in patients with juvenile forms of hypophosphatasia (HPP), resulting in a no added benefit rating for that patient sub-population.

In the UK, given the single-arm trial design and lack of robust long-term data, NICE guidance stipulated a managed access arrangement restricting access for patients with juvenile-onset disease with starting and stopping criteria and requiring further data collection to address uncertainties in the clinical evidence.

KANUMA gained EMA approval based on open-label single-arm studies measuring the overall survival of patients with LAL deficiency compared to a historical cohort of untreated patients with LAL deficiency and similar clinical characteristics.

Despite the small trial size (N=11 patients), HAS viewed the survival benefit relative to the historical control as significant for patients with infant-onset LAL deficiency, leading to an ASMR III rating.

For non-infant-onset LAL patients, biomarker endpoints, rather than survival rate, were collected, including normalization of alanine aminotransferase (ALT) levels, with the weaker data package, as well as lack of relevant QoL data and potential safety risks, resulting in an ASMR V rating.

Though NICE's assessment recognized the efficacy of KANUMA in treating rapidly progressive disease in the short-term, the unclear long-term benefit in patients and exceptionally high price of KANUMA, even with the proposed per-patient cost cap, resulted in a negative recommendation for reimbursement.

XIAPEX was approved by the EMA based on a placebo-controlled phase 3 trial measuring the percentage of patients experiencing symptom improvement (reduction of contracture to ≤5º) 30 days after treatment.

HTA bodies across EU3 countries rejected the use of a placebo control group, citing percutaneous needle fasciotomy (PCNF), a non-pharmacological intervention, as the appropriate treatment comparator.

As a result of the lack of appropriate comparator and without an orphan designation, XIAPEX received a no added benefit rating in Germany; similarly, a negative HTA outcome was assigned in France (SMR Insufficient) and NICE's guidance on XIAPEX was withdrawn in the UK.

Product	Follow-Up Studies	Follow-Up Data Acceptability DEU	Follow-Up Data Acceptability FRA	Follow-Up Data Acceptability GBR	Additional Supporting Evidence	Supporting Evidence Acceptability DEU	Supporting Evidence Acceptability FRA	Supporting Evidence Acceptability GBR
Palynziq	N/A	–	–	N/A	N/A	–	–	N/A
LUXTURNA	Data at 3- to 4-year follow-up from the phase 3 RCT	–	✓	✓	N/A	–	–	–
Strensiq	Extension studies, with N=10 patients and N=12 patients each, for up to 5 years	–	–	×	Retrospective non-interventional studies to assess survival, need for invasive ventilation; Comparative analysis with historical control patients	✓	✓	✓
Kanuma	Open-label follow-up period of 130 weeks	–	✓	×	Comparison of 12-month death rates from the single-arm study with data from a historical control	✓	✓	×
XIAPEX	Data at 5-year follow-up from the phase 3 RCT	–	✓	N/A	N/A	–	–	N/A

Accepted · Neutral · Not Accepted

FIGURE 4: SUMMARY OF ADDITIONAL SUPPORTING EVIDENCE SUBMITTED FOR EACH PRIORITIZED ANALOGUE

CONCLUSIONS

4 of the 5 analogues analyzed had an orphan designation and all analogues assessed were coming in the market as sole pharmacological treatments for the diseases. Despite the lack of approved SoC and high unmet need, HTA bodies expected the appropriate comparators to be used, the long-term benefit of the therapy to be demonstrated, and placed the most emphasis in symptom control and prevention of disease progression (FIGURE 5).

Our research showed that HTA bodies such as G-BA and HAS expect a comparison with SoC to be used even if the SoC is not a pharmacological agent. For example, XIAPEX did not provide data in comparison to the standard surgical procedure (PCNF) and thus was not able to prove comparative effectiveness in Germany and France.

In the cases where no other treatment option was available and a single-arm study design was used, historical comparisons were submitted and were accepted in France and Germany. In the UK however, NICE highlighted the limited robustness of such comparisons, citing differences in patient populations across studies and differences in the data collection methodology.

The analysis also showed that OS extension was considered a key value driver, but HTA bodies acknowledged that some of these therapies are not curative and therefore placed greater emphasis on symptom control and management of disease progression. In the case of PALYNZIQ for example the lack of QoL endpoints that measure improvement in neurocognitive symptoms was negatively perceived across EU3 markets.

Finally, durability of effect was seen as the most important value attribution factor in the assessment of these analogues. Since the majority of the trials were a in the range of 24 weeks long, 4 out of 5 of the selected analogues submitted follow-up studies to ensure robustness of clinical evidence. Other concerns regarding the validity of the follow up studies reflected uncertainties around the population sample of the follow up being identical to that of the original trial. Discrepancies between patient characteristics weakened the validity of long-term results, which was reflected in the imposition of stopping and starting criteria as well as severe discounts.

Value Drivers	Impact on HTA	XIAPEX	Kanuma	Strensiq	LUXTURNA	Palynziq
Comparison with Local SoC	◔	○	○	○	✓	✓
Durability of Effect	●	×	✓	✓	✓	–
Extent of Survival Benefit	◕	○	✓	✓	○	○
Symptom Improvement	◑	–	–	✓	✓	–
Unmet Need	◔	✓	✓	✓	✓	✓

Lower ◔ ◑ ◕ ● Higher

✓ Positively perceived · – Neutral · × Negatively perceived · ○ Evidence not submitted

FIGURE 5: KEY VALUE DRIVERS AND ESTIMATED IMPACT ON HTA OUTCOMES

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