CELL & GENE THERAPY INSIGHTS

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SPOTLIGHT

COMMENTARY

Health Technology Assessment of Gene Therapies in Europe and the USA: Analysis and Future Considerations

Tingting Qiu, Eve Hanna, Monique Dabbous, Borisov Borislav & Mondher Toumi

Gene therapies constitute a new concept of transformative therapies, administered once in a lifetime. The value assessment of these innovative therapies constitutes a challenge for health technology assessment (HTA) bodies. The HTA reports for all seven gene therapies that have to date been granted a market authorization in the European Union (EU) and/or the United States (US) were examined to understand the rationale behind their assessment outcomes and to explore the differences in value assessment across US, England, Scotland, France and Germany. In England, Imlygic® was accepted for use with the manufacturer agreeing to the application of a discount to the list price under a patient access scheme (PAS), while Strimvelis® was recommended due to its cost–effectiveness estimate being considered as reasonable under the highly specialized technology (HST) evaluation. KYMRIAH® and Yescarta® were approved for use within the Cancer Drugs Fund (CDF) in England, conditionally, as long as managed access agreements are upheld. In France, KYMRIAH®, Yescarta®, and Luxturna® were considered as having important actual clinical benefit. In France, GLYBERA® was considered to have ‘insufficient’ benefit due to its unsustainable and heterogeneous treatment effects. In Germany, the extent of the added benefit of GLYBERA®, KYMRIAH®, and Yescarta® was evaluated as ‘non-quantifiable’ as the submitted evidence made reliable, comparative assessments difficult. In Germany, Imlygic® was assessed to have no added benefit due to the selection of inappropriate comparators. In Scotland, KYMRIAH® was accepted for B-cell acute lymphoblastic leukemia treatment with a PAS, while Yescarta® and KYMRIAH® for diffuse large B-cell lymphoma were rejected due to unjustified cost–effectiveness estimates. In the USA, KYMRIAH®, Yescarta®, Luxturna®, and Zolgensma® were evaluated as having substantial net health benefits, however, a high certainty of conclusion for the assessment of Zolgensma® was established. Although the limitations in pivotal studies resulted in substantial uncertainties regarding long-term treatment benefit, there was still a possibility for gene therapies to gain acceptance from HTA bodies. Most importantly, further evidence collection becomes the critical key, not only to reduce the uncertainty in reimbursement decisions, but also to increase the public's confidence in the use of gene therapies.

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INTRODUCTION

Advanced therapy medicinal products (ATMPs) have transformed the disease treatment paradigm, not only alleviating disease symptoms but targeting the primary cause of diseases and curing them through single or short/limited term therapy administration [1]. Regulators have introduced a series of proactive strategies to accelerate the market approval of ATMPs through the adoption of flexible evidence assessment approaches and the implementation of expedited programs [2].

Despite an expanding number of ATMPs with regulatory approval (Table 1), addressing the uncertainties around the value and its impact on pricing and reimbursement decisions of ATMPs remains challenging [3]. ATMPs are generally considered to be costly, partly as a result of the high cost of development, manufacturing, and clinical administration. The coverage decisions are commonly driven by value assessment conducted by Health Technology Assessment (HTA) bodies, which tend to hold a more conservative attitude towards the appreciation of ATMPs as only scarce evidence is available to determine their long-term clinical benefit [4]. Furthermore, it is important to note that payers in the different countries have different perspectives on value appreciation and willingness-to-pay for certain values [5]. Such inconsistences in value appreciation will probably lead to disparity in reimbursement and pricing decisions.

This discussion paper aims to review HTA reports for gene therapies in 5 countries, including the USA, the United Kingdom (England and Scotland), France, and Germany (Table 2). The HTA reports were retrieved from the Institute for Clinical and Economic Review (ICER) [6] in the USA, the National Institute for Health and Care Excellence (NICE) [7] in England in the UK, the French National Authority for Health (HAS) [8] in France, the Federal Joint Committee (G-BA) [9] in Germany, and the Scottish Medicine Consortium (SMC) [10] in Scotland. Furthermore, this paper examines

TABLE 1

Gene therapy with market authorization in European Union and the USA.

Approved country	Brand name	Active substance	Indication	Date of market authorization	Market authorization pathway	Status
EU	GLYBERA®	Alipogene tiparvovec	Familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions	25/10/2012	Approval under exceptional circumstance	Withdrawn (28/10/2017)
EU	Imlygic®	Talimogene laherparepvec	Unresectable metastatic melanoma	16/12/2015	Standard approval	Authorized
EU	Strimvelis®	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cdna sequence	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	26/05/2016	Standard approval	Authorized
USA, EU	KYMRIAH®	Tisangenlecleucel	▸ Relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL)	USA: 30/08/2017 EU: 22/08/2018	USA: priority review, breakthrough designation (BTD)	Authorized
			▸ Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	USA: 13/04/2018 EU: 22/08/2018	EU: priority medicine (PRIME)	
USA, EU	Yescarta®	Axicabtagene ciloleucel	DLBCL and primary mediastinal B-cell lymphoma after two or more systemic therapies	USA: 18/10/2017 EU: 23/08/2018	USA: priority review, BTD EU: PRIME	Authorized
USA, EU	Luxturna®	Voretigene neparvovec	Biallelic RPE65 mutation-associated retinal dystrophy	USA: 19/12/2017 EU: 22/11/2018	USA: priority review, BTD	Authorized
USA	Zolgensma®	Onasemnogene abeparvovec-xioi	Pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene	24/05/2019	USA: priority review, BTD	Authorized

TABLE 2

HTA decisions for Gene therapy approved in Europe and the USA.

Brand name	Health technology assessment decisions in each country				
	France	Germany	England	Scotland	USA
GLYBERA®	Not recommended (SMR*: insufficient)	Recommended (Added benefit: proven; Extent of added benefit: non-qualifiable)	NA	NA	NA
Imlygic®	NA	Recommended (Added benefit: no; Extent of added benefit: no)	Recommended with patient access scheme	Not recommended: in the absence of submission of MA holder	NA
Strimvelis®	NA	NA	Recommended	NA	NA
KYMRIAH®	Recommended for hospital use for both indications. ▸ B-cell ALL (SMR: important, ASMR: III); ▸ DLBCL (SMR: important, ASMR: IV)	Recommended for both indications. (Added benefit: proven Extent of added benefit: non-unqualifiable)	Recommended for use within CDF for both indications, along with market access agreement	▸ B-cell ALL: recommended with patient access scheme ▸ DLBCL: not recommended	▸ At least a small net health benefit ▸ ICER met the cost–teffectiveness threshold
Yescarta®	Recommended for hospital use for both indications (SMR: important, ASMR: III)	Recommended for both indication (Added benefit: proven; Extent of added benefit: non-qualifiable)	Recommended for use within CDF for both indications, along with market access agreement	Not recommended for neither indications	▸ At least a small net health benefit ▸ ICER met the cost–effectiveness threshold
Luxturna®	Recommended for hospital use (SMR: important; ASMR: II)	Ongoing	Ongoing	Ongoing	▸ At least a small net health benefit ▸ ICER higher than the cost–effectiveness threshold
Zolgensma®	NA	NA	NA	NA	▸ High possibility to have a substantial net health benefit. ▸ ICER higher than the cost–effectiveness threshold

ASMR: The Improvement of Medical Benefit; ALL: Acute lymphoblastic leukemia; CDF: Cancer Drugs Fund; DLBCL: Diffuse large B-cell lymphoma; ICER: Incremental Cost-Effectiveness Ratio; NA: Not Applicable; SMR: The Medical Benefit.

and discusses the differences in value appreciation processes across these five countries to explore the impact of these factors on the reimbursement decision-making for gene therapies.

HEALTH TECHNOLOGY ASSESSMENT FOR SEVEN GENE THERAPIES

GLYBERA® (alipogene tiparvovec)

GLYBERA®, for the treatment of adult patients with familial lipoprotein lipase (LPL) deficiency who have severe or multiple pancreatic crises despite a low-fat diet, was reviewed by the HAS in France and by the G-BA in Germany. GLYBERA® was withdrawn from EU on 28 October 2017 since the MA holder decided not to apply for a renewal of MA.

France: HAS

The HAS stated that the actual benefit of GLYBERA® was insufficient (SMR: insufficient) to be recommended in the list of reimbursable products for the following reasons: 1) moderate effect on the blood triglyceride level was not maintained beyond one year, and the patient responses to treatment were heterogeneous; 2) no proof that GLYBERA® had an impact in the prevention of pancreatitis; 3) uncertainties about its short- and medium-term safety due to its complex mode of administration. Taking the limitations in methodology (open, before/after, small patient number, questionable primary efficacy endpoint) into account, the benefit of GLYBERA® could not be established [11].

Germany: G-BA

The G-BA evaluated the extent of added benefit of GLYBERA® as 'non-quantifiable' because the data provided by manufacturers did not permit a reliable assessment. The G-BA pointed out that the pivotal studies had a high risk of bias in study design and outcomes. The study populations and dosage regime only partially complied with approved label. In line with the European Medicines Agency's request for the establishment of a patient registry and further data collection regarding its efficacy and safety, the G-BA's decision was only valid for one year, at which time the re-evaluation of GLYBERA® would begin based on the new evidence collected [12].

IMLYGIC® (TALIMOGENE LAHERPAREPVEC)

Imlygic® for the treatment of unresectable, regionally or distantly metastatic melanoma has been evaluated in England and Germany. NICE considered it to be cost-effective when compared with available treatments other than immunotherapies, while the G-BA assessed Imlygic® to have no added benefit due to the use of an inappropriate comparator from the G-BA perspective.

The United Kingdom: England: NICE

Not the same as the indication approved by EMA, NICE

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recommended that the use of Imlygic® should be restricted to adult patients whose diseases were not suitable for immunotherapies. As agreed in the patient access scheme, the manufacturing company must apply a discount to Imlygic®'s list price. Imlygic® was proven to have a significant improvement in overall survival and complete response compared with an ineffective treatment (GM-CSF). However, a reliable assessment for the effectiveness of Imlygic® against currently used immunotherapies (such as ipilimumab) was difficult due to a lack of evidence. This made the ICER appreciation for Imlygic® versus immunotherapies impossible. Nevertheless, NICE considered Imlygic® to be cost-effective compared to dacarbazine and the best supportive care [13].

Germany: G-BA

The G-BA distinguished between three treatment populations: 1) treated naïve adults with BRAF V600 mutant tumor, 2) treated naïve adults with BFAR V600 wild type tumor; and 3) pre-treated adults. The German HTA body also specified a different, appropriate comparator therapy for each treatment population. The manufacturer-selected comparator, GM-CSF, did not concur with any of the research questions and was not approved for the treatment of melanoma. The Institute for Quality and Efficiency in Health Care (IQWIG), which advises the G-BA, considered that no studies allowing for an indirect comparison with the appropriate comparator therapy were presented. As no suitable data from which an added benefit could be derived was available, an added benefit of Imlygic® was not proven [14].

STRIMVELIS®

Strimvelis® for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) has been evaluated in England only. Additionally, Italy, as the only country with a licensed manufacturing center for Strimvelis®, also agreed to reimburse it with a pay for performance deal.

England: NICE

NICE has recommended Strimvelis® as an option for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). Strimvelis® was considered as a highly specialized technology (HST) due to the ultra-rare nature of its target disease and its innovative mechanism of action. Despite the uncertainty in small patient number and uncontrolled study design, NICE determined that Strimvelis® showed clinical benefits in improving survival and reconstituting the patients' immune system. Moreover, its advantages over hematopoietic stem cell transplantation (HSCT) in terms of lower risk of post-treatment mortality and the lack of graft-versus-host disease (GvHD) were also appreciated. NICE believed that Strimvelis® had an ICER lower than the cost–effectiveness threshold (£100,000 per QALY gained) that is commonly considered as acceptable as a HST, even when several health-related benefits and wider benefits of Strimvelis® were not captured in the economic analysis [15].

KYMRIAH® (Tisagenlecleucel)

KYMRIAH®, indicated for the treatment of B-cell acute lymphoblastic leukaemia (ALL) and for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), has been evaluated in five countries (UK, France, Germany, Scotland, and the USA). It is reimbursed for both indications in four countries (England, France, Germany, and the USA). In Scotland, KYMRIAH®, was reimbursed for the treatment of B-cell ALL, yet failed to be accepted for the treatment of DLBCL.

The United Kingdom: England: NICE

NICE recommended KYMRIAH® for both indications in the treatment of B-cell ALL and DLBCL, with funding from the Cancer Drugs Fund (CDF) via a managed entry agreement detailing the conditions of the recommendation [16,17]. The CDF provides interim funding for promising new cancer treatments in order to facilitate patient access, primarily where NHS, based on NICE recommendation, is unwilling and/or unable to fund [18]. The cost–effectiveness estimate for KYMRIAH® was higher than the threshold which NICE normally considers as acceptable. Therefore, KYMRIAH® was not recommended for routine use in England. Additional data will be collected from ongoing clinical trials (ELIANA study for B-cell ALL patients and JULIET study for DLBCL patients) and from UK routine, population-wide public health databases to address uncertainties surrounding: 1) more mature data to support its curative nature; 2) rate of subsequent stem cell transplant (in case of B-cell ALL); 3) the number of patients who will need intravenous immunoglobulin treatment and the treatment duration. NICE will begin a review of the current guideline once the additional data becomes available.

The United Kingdom: Scotland: SMC

The SMC recognized KYMRIAH®'s higher overall remission rate compared with historical controls in the treatment of B-cell ALL indicated in the pivotal ELIANA study, and agreed to accept greater uncertainty in the economic analysis of an ultra-orphan drug. KYMRIAH® was accepted for reimbursement in B-cell ALL treatment with the implementation of Patient Access Scheme (PAS) to improve its cost–effectiveness. Additionally, opinions from the Patient and Clinical Engagement (PACE) process were also taken into account. They concluded that, as a potentially life-extending and even curative treatment, KYMRIAH® could help reduce the emotional burden and improve overall quality of life for B-cell ALL patients [19]. However, KYMRIAH® was not recommended for DLBCL because the treatment cost in relation to its health benefits was not sufficiently justified, in addition to a lack of robust economic analysis [20].

France: HAS

The HAS has considered KYMRIAH® to have a high actual clinical benefit (SMR: important) and a moderate clinical added benefit (ASMR: III) for the treatment of

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B-cell ALL based on the evidence that high rates of complete remission were achieved in both the ELIANA and ENSIGN studies (approximately 67% in the intention to treat population) [21]. The HAS also assessed KYMRIAH® as having a high actual clinical benefit (SMR: important) and a minor clinical added value (ASMR: IV) for the treatment of DLBCL [22]. HAS suggested that the precise quantification of clinical benefits was difficult due to the lack of comparative studies versus existing treatments. Uncertainties remained in the persistence of efficacy, long-term safety and the impact of complex treatment process on actual efficacy. Health authorities at HAS further pointed out that the administration of KYMRIAH® should only be limited to a small number of qualified healthcare institutions.

Germany: G-BA

The added benefit of KYMRIAH® in both B-cell ALL and DLBCL was considered to be already proven due to its orphan drug status within German regulation in early benefit assessment. The G-BA evaluated the extent of additional benefit of KYMRIAH® for the treatment of B-cell ALL and DLBCL as 'non-quantifiable' due to data scarcity and the uncertainty in short follow-up duration, incomplete patient recruitment, the impact of bridging therapy (chemotherapy received before KYMRIAH® treatment), and the indirect comparison with historical evidence [23,24].

USA: ICER

ICER stated that the uncertainty in a non-comparative study with small patient size and short follow-up made it difficult to evaluate the magnitude of health benefit compared to other therapies. However, considering KYMRIAH®'s superior efficacy and manageable adverse effects, ICER did recognize that it at least offered a small net health benefit compared with current salvage chemotherapy in both B-cell ALL and DLBCL patients. KYMRIAH® was, therefore, considered to provide clinical benefits in terms of the improvement of Quality-Adjusted Life-Years (QALYs) and the survival rate versus the comparator, and meeting the commonly cited cost–effectiveness threshold in the USA ($150,000 per QALY) [25].

YESCARTA® (AXICABTAGENE CILOLEUCEL)

Yescarta® for the treatment of diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) has been evaluated in 5 countries (UK – England, UK – Scotland, France, Germany, and the USA).

England: NICE

NICE recommended Yescarta® for use within the CDF along with a managed access agreement outlining the conditions of the recommendation. Yescarta® met NICE's requirements for a life-extending treatment at the end of life. NICE recognized its clinical benefits shown in increasing patients' survival (overall or progression-free) and response rates. However, the exact magnitude of Yescarta®'s benefit was unknown due to the limitation regarding short follow-up duration and the non-comparative design of pivotal study. NICE requested that further data be collected from ongoing clinical trial (ZUMA-1) in order to reduce the uncertainty in survival (overall and progression-free) and immunoglobulin use until February 2022. Once this data is obtained and made available, NICE will re-evaluate whether it should be recommended for use and update the current guidance accordingly [26].

France: HAS

HAS considered Yescarta® had a high actual clinical benefit (SMR: important) and a moderate clinical added benefit (ASMR: III) for both indications [27], unlike KYMRIAH®. This assessment was made primarily relying on the results of ZUMA-1 study, in which Yescarta® showed potential clinical benefits in complete response rate and 18-month survival rate. However, HAS requested that further data be collected and provided to address the uncertainties regarding the efficacy, safety, and complexity of the treatment process. Yescarta®'s use should be restricted to a small number of specifically qualified centers.

Germany: G-BA

The added benefit of Yescarta® was considered as proven due to its orphan drug status, while the extent of added benefit of Yescarta® was evaluated as 'non-quantifiable'. As suggested in the SCHOLAR-1 study, the G-BA acknowledged that Yescarta® had a potential advantage in improving the overall survival for both DLBCL and PMBCL patients. Considering the disease severity and poor prognosis, the improvement in overall survival could be of high meaning. However, due to the limitation regarding indirect historical comparison and further uncertainty in the ZUMA-1 study, the comparative assessment for other outcomes on morbidity, adverse effects, and quality of life was not possible. The decision made by the G-BA will remain valid until the 15th of May, 2022, at which time the G-BA will update the benefit assessment of Yescarta® based on new evidence, which could be generated from an ongoing clinical trial (such as the 60-month data of the ZUMA-1 study) or prospective comparative studies beyond the pivotal trial [28].

Scotland: SMC

Despite the advice from PACE process that Yescarta® could potentially achieve a durable response and be a life-extending treatment option, the SMC did not recommend its use in Scotland. It was not accepted as the SMC considered that the limitations in ZUMA-1 study (study design and no subgroup analysis) and SCHOLAR-1 (bridging chemotherapy, population heterogeneity and no baseline data) caused uncertainty in Yescarta®'s long-term benefits. Although the SMC agreed to accept more uncertainty in the economic analysis of ultra-orphan medicines, they claimed that Yescarta®'s cost in relation to its long-term benefits was not sufficiently justified [29].

The USA: ICER

ICER evaluated that the net health benefit of Yescarta® might be substantial as it showed clinical advantages

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in terms of complete remission rate, disease-free survival, and overall survival compared with other therapies. While the certainty for this conclusion was low due to limitations of non-comparative trial with small size and short follow-up, Yescarta®'s clinical benefits contributed to a cost–effectiveness estimate that met the commonly cited cost–effectiveness threshold in the USA [25].

LUXTURNA® (VORETIGENE NEPARVOVEC)

Luxturna® for the treatment of inherited retinal dystrophies caused by RPE65 gene mutations has been evaluated in France and the USA. The assessment in the UK, Germany, and Scotland is currently ongoing and expected to be published in late 2019 or early 2020.

France: HAS

The HAS considered Luxturna® to have a high actual clinical benefit (SMR: important) and an important clinical added benefit (ASMR: II). This assessment was made based on its proven efficacy in a pivotal Phase 3 study. Moreover, disease severity, rarity, and the unavailability of alternative treatments for the target disease were also key factors for this positive recommendation. HAS requires that the treatment be limited to specialized institutions, with treatment decisions made by multidisciplinary consultation meetings and based on a set of medical examinations. Follow-up studies to collect data on patient characteristics, treatment patterns, conditions of use, long-term efficacy, safety, and impact on quality of life must also be conducted. The HAS will re-evaluate the drug benefit once the 5 years of data collection has been completed [30].

USA: ICER

ICER evaluated Luxturna® to have significantly improved health outcomes compared to the standard of care (SoC), while potential harms related to surgical aspects of administration were also considered. Therefore, Luxturna® was found to provide, at least, a small net health benefit. The high cost made it unlikely to be a cost-effective intervention at the commonly used cost–effectiveness threshold in the USA [31]. However, inclusion of the indirect and non-medical costs would decrease the total incremental cost and, therefore, the corresponding cost–effectiveness ratio. ICER recognized uncertainty around the relevance of the primary endpoint in the real-world setting, as well as its long-term effect on retinal degeneration.

ZOLGENSMA® (ONASEMNOGENE ABEPARVOVEC)

Zolgensma® for the treatment of spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron (SMN) 1 gene has been evaluated by ICER in April 2019. This evaluation was updated on May 24th, 2019 to align with the Food and Drug Administration (FDA) approval.

USA: ICER

Zolgensma® was found to improve motor function, survival, and reduce the needs for permanent ventilator support. Despite the limitation of a single-arm, open label study with small patient number, ICER had high certainty that Zolgensma® would provide a substantial net health benefit [32]. The value-based price benchmark of Zolgensma® would be $1.1–1.9 million in order to meet the commonly cited cost–effectiveness threshold ($100,000–150,000) from the QALY perspective, but a higher price ($1.2–2.1 million) could be possible to achieve if the alternative threshold for cost per Life-Year (LY) gained was used. The limitation in study design raised concerns in the generalizability of results to a broader population as well as the possibility in treatment effect overestimation as seen in single arm trials.

CONCLUSION: DISCREPANCY IN THE HEALTH TECHNOLOGY ASSESSMENT OF GENE THERAPY

Gene therapies have usually been approved based on short-term clinical data derived from non-comparative, open-labelled studies with short follow-up durations and small patient populations. Such limitations in pivotal clinical trials methodology have led to uncertainties regarding gene therapies' long-term efficacy and safety and furthermore, have made the precise assessment of gene therapy' benefit and cost–effectiveness challenging.

Value appreciation

In general, value appreciation constituted one of the most important factors for the reimbursement decisions (Table 3), while different countries showed varying perspectives on the weights allocated to each attribute [33].

France emphasized clinical effectiveness, disease severity and rarity as well as the unmet medical needs of the disease area and patients, as can be seen in the fact that all recommended gene therapies (KYMRIAH®, Yescarta®, and Luxturna®) were evaluated as having 'important' actual clinical benefit.

Germany underlined the comparative benefits against available treatments. Therefore, the limitations of indirect historical comparison were mentioned as one of the important reasons for the unavailability of accurate benefit assessments for GLYBERA, KYMRIAH® and Yescarta®. Not surprisingly, Imlygic® was evaluated with no added benefit due to the inappropriateness of comparator from G-BA perspective.

In the UK (England and Scotland), as in the USA, great importance is attached to cost–effectiveness analysis. NICE defined a higher ICER threshold for ultra-orphan drugs evaluated under the HST pathway. The SMC introduced a new approach for the assessment of ultra-orphan drugs, in which a higher uncertainty in economic analysis could be acceptable. This was the case with Strimvelis® for ADA-SCID treatment in England, as well as KYMRIAH® for B-cell ALL treatment in Scotland.

Reimbursement & affordability strategies

Along with the disparity in value assessment, different strategies were adopted in each country to achieve prompt market access to innovative

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TABLE 3

The uncertainty in available evidence identified by HTA body.

Branch name	Uncertainty existed in the submitted evidence
GLYBERA®	▸ HAS: short and medium-term safety accompanying with the complex administration process ▸ G-BA: bias resulted from included population and dosage regime in pivotal studies
Imlygic®	▸ NICE: comparative effectiveness against currently used immunotherapies ▸ G-BA: comparators were not relevant to research questions and not approved for use in same indication
Strimvelis®	▸ NICE: limited evidence for comparator
KYMRIAH®	▸ HAS: long-term efficacy and safety; impact of complex administration process ▸ G-BA: incomplete patient recruitment, the influence of bridging therapy and historical comparison ▸ SMC: the justification of cost in relation to the health benefit
Yescarta®	▸ HAS: long-term efficacy and safety; impact of complex administration process ▸ G-BA: the effect on morbidity, adverse effects and quality of life compared to other therapies ▸ SMC: questionable study design (no subgroup analysis, population heterogeneity and lack of baseline data) ▸ NICE: the exact magnitude of treatment benefit on survival rate and immunoglobulin use
Luxturna®	▸ HAS: long-term efficacy, safety and impact on quality of life ▸ ICER: the validity of primary endpoint, and effect on retinal degeneration
Zolgensma®	▸ ICER: the generalizability of results; the possibility of effect exaggeration

G-BA: the Federal Joint Committee; HAS: Haute Autorité de Santé; ICER: The Institute for Clinical and Economic Review; NICE: The National Institute for Health and Care Excellence; SMC: The Scottish Medicines Consortium.

gene therapy without impairing healthcare affordability by including costly yet effective treatments in the reimbursement list [34].

In England, all gene therapies except Strimvelis® were recommended for use in combination with a commercial PAS in order to improve the cost–effectiveness profiles. Additionally, despite negative recommendations for routine use in England, two chimeric antigen receptor T cell therapies, KYMRIAH® and Yescarta®, were accepted for interim use in the CDF during further data collection period.

In France, all reimbursed gene therapies were restricted to be administered in qualified healthcare institutions. Moreover, the prescription decision for Luxturna® must be examined by a multi-discipline expert panel, and the HAS will re-evaluate Luxturna®'s benefit after five years based on new evidence.

In Germany, the G-BA holds a conservative attitude in the assessment of extent of added benefit, which is reflected in the fact that all gene therapies (except for Imlygic®) were considered to have 'non-quantifiable' added benefit. Additionally, all the assessments were valid for a limited time, with re-evaluation beginning after additional data collection is completed.

TABLE 4

The description of pivotal studies for seven gene therapies.

Study design	Patient size	Primary endpoints	Register number in clinicaltrail.gov
KYMRIAH®			
- For B-cell ALL			
▸ ELIANA study: Phase 2, single-arm, open-label	81	Overall remission rate per IRC assessment	NCT02435849
▸ ENSIGN study: Phase 2, single-arm, open-label	64	Overall remission rate 1) per IRC assessment 2) per local Investigator assessment	NCT02228096
- For DLBCL			
▸ JULIET study: Phase 2, single-arm, open-label	167	Overall response rate	NCT02445248
Luxturna®			
▸ Study 301: Phase 3, randomized control, open-label study; control group: patients receiving no intervention	31	Multi-luminance Mobility Testing (MLMT), Bilateral	NCT00999609
Zolgensma®			
▸ CL-101 study: Phase 1, single-arm, two cohorts, open-label	15	Number of Participants 1) experienced one grade III or higher unanticipated, treatment-related toxicity; 2) requirement of ≥16-hour respiratory assistance per day ≥2 weeks; 3) CHOP-INTEND score	NCT02122952
▸ STR1VE study: ongoing Phase 3 study: single-arm, open-label	20	1) The proportion of patients achieving the milestone of sitting without support for at least 30 seconds at 18 months of age 2) survival at 14 months of age	NCT03306277
▸ START study: observational, long-term follow up study up to 5 years	15	Long-term safety	NCT03421977
Imlygic®			
▸ OPTiM Study (Study 005/05): Phase 3, randomized, controlled, open-label study; Control group: GM-CSF	437	Durable response rate (defined as the rate of objective response, complete or partial)	NCT00769704

ALL: Acute Lymphocytic Leukemia; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DLBCL: Diffuse Large B-cell Lymphoma; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; IRC: Independent Review Committee.

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TABLE 4 CONTINUED

The description of pivotal studies for seven gene therapies.

Study design	Patient size	Primary endpoints	Register number in clinicaltrail.gov
Strimvelis®			
Study AD1115611: Phase 1/2, single-arm, open label	12	Survival rate up to 1 year	NCT00598481
Yescarta®			
ZUMA-1 study: Phase 1/2, single-arm, open label	118	Percentage of participants experiencing adverse events; overall response rate	NCT02348216
SCHOLAR-1 study: multi-cohort, retrospective, pooled analysis data from two randomised controlled studies and two retrospective databases; Control group: salvage chemotherapies	636	Response rate, complete response and overall survival	Not available
GLYBERA®			
CT-AMT-010-01 study: single-arm, open-label, dose-escalating study	8	Reduction of fasting triglyceride (TG) concentrations; toxicity	Not available
CT-AMT-011-01 study: single-arm, open-label, dose-escalating study	14	Reduction of fasting triglyceride (TG) concentrations; toxicity	NCT01109498
CT-AMT-011-02 study: single-arm, open-label study	5	Reduction of fasting triglyceride (TG) concentrations; toxicity	NCT00891306

ALL: Acute Lymphocytic Leukemia; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DLBCL: Diffuse Large B-cell Lymphoma; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; IRC: Independent Review Committee.

In Scotland, the SMC took more precautions in the reimbursement of gene therapies with unjustified cost–effectiveness, which resulted in negative recommendations in DLBCL for Yescarta® and KYMRIAH®. Although additional factors including disease rarity, opinions from other stakeholders (such as patient advocacy organizations) and the implementation of a PAS were also considered, economic analysis remained the key determinant for reimbursement decision-making.

Clinical trials methodology & further data collection requirements

Apart from the commonly cited study limitations (single-arm, open label, small patient number, and short follow-up) in pivotal studies, some additional weaknesses in study methodologies were also noticed in certain countries. For example, the SMC indicated concerns for population heterogeneity in the SCHOLAR-1 study, while ICER doubted whether the primary endpoint used in the Phase 3 study for Zolgensma® would be well correlated with outcomes in real-world setting (Table 3). This indicated payers' insights on areas for improvement in clinical trial design and what evidence will still be required in the future to minimize uncertainties. However, there were differences with regards to the uncertainty that most concerned the payers across the countries included in this study. This suggests that further data collection must take into consideration the different evidence requirements on a country-by-country basis, thus, the administration burden for manufacturers may not be negligible [35].

TRANSLATION INSIGHTS

Substantial limitations in the study methodology have raised concerns regarding the long-term efficacy and safety for most gene therapies. Various approaches were used by different HTA bodies to minimize the potential risk of accepting costly gene therapies with uncertain outcomes or severe impact on the reimbursement list. England was able to use side pathways to reimburse such products, via the HSTC and the CDF. Germany has relied on a law that systematically grants added benefit for orphan designated products. France has shown an unusually generous attitude towards gene therapies. Scotland has used modifiers for orphan drugs to boost the access of gene therapies.

One way or another, all countries have considered a reassessment as more data is collected in the real world to inform future decisions in continuing to maintain the reimbursement of these gene therapies. One must acknowledge that despite the evidence presented by gene therapy manufacturers not matching the standard requirements of HTA agencies - having no comparative studies with single arm trials, short term durations, and surrogate endpoints in some cases (Table 4) – to date, most gene therapies have successfully gained reimbursement. It is doubtful these therapies would have been as successful in achieving these favorable results had they not been gene therapies.

It is unclear how long such favorable attitude towards these gene therapies will endure. However, it is sending a strong positive signal to manufacturers that payers are open to such innovation and face some informal resistance to refuse access to gene therapies.

AUTHORSHIP & CONFLICT OF INTEREST

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AFFILIATIONS

Tingting Qiu
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Eve Hanna
Creativ-Ceutical, 215, rue du Faubourg St-Honoré, 75008 Paris, France

Monique Dabbous
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Borislav Borissov
Prescriptia 28, Hristo Botev Blvd, Sofia, Bulgaria

Mondher Toumi
Author for correspondence
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France
mondher.toumi@univ-amu.fr