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Health Policy Analysis

Financing and Reimbursement of Approved Advanced Therapies in Several European Countries

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ABSTRACT

Objectives: The uncertainty in the cost-benefit of advanced therapy medicinal products (ATMPs) is a current challenge for their reimbursement in health systems. This study aimed to provide a comparative analysis of the National Health Authorities (NHAs) reimbursement recommendations issued in different European countries.

Methods: The NHA reimbursement recommendations for the approved ATMPs were compared among 8 European Union (EU) Countries (EU8: Ireland, England/Wales, Scotland, The Netherlands, France, Germany, Spain, and Italy). The search was carried out until December 31, 2021.

Results: A total of 19 approved ATMPs and 76 appraisal reports were analyzed. The majority of the ATMPs were reimbursed, although with uncertainty in added therapeutic value. No relationship between the type of the European Medicines Agency approval and reimbursement was found. Managed entry agreements, such as payment by results, were necessary to ensure market access. The main issue during the evaluation was to base the cost-effectiveness analyses on assumptions because of the limited long-term data. The estimated incremental cost-effectiveness ratio among countries reveals high variability. Overall, the median time to NHA recommendation for the EU8 is in the range of 9 to 17 months.

Conclusions: Transparent, harmonized, and systematic assessments across the EU NHAs in terms of cost-effectiveness, added therapeutic value, and grade of innovativeness are needed. This could lead to a more aligned access, increasing the EU market attractiveness and raising public fairness in terms of patient access and pricing.

Keywords: added therapeutic value, advanced medicinal products, financing government, health technology assessment, market access.

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Introduction

Advanced therapy medicinal products (ATMPs) are innovative drugs, based on genes, cells, and tissues, offering potentially curative treatment options for a range of diseases. ATMPs are associated with high costs and, for some of them, uncertain efficacy claims, which is being a current setback for the market access of these drugs.[1] This is accentuated by the fact that an increased number of ATMPs are expected to enter the market in the coming decade, covering indications with higher prevalence rather than orphan diseases.[2,3] Once the European Commission (EC) approves an ATMP, the access to treatment depends on the inclusion of the product in the public healthcare funding. Each European Member State has its own authority over the market access of new products and its reimbursement agreements, which are conditioned by the respective healthcare resources. With this purpose, the National Health Authorities (NHAs) of European Member States perform a relative efficacy and safety assessment, giving recommendations on whether a product should be considered for reimbursement and under what conditions, if necessary.[4] These NHAs appraisals usually consider several criteria to make their recommendations, such as the burden and severity of the target indication, the relative effectiveness and safety of the new product compared with the standard of care (SoC) or best supportive care, the cost and economical effectiveness, as well as ethical, social, and patient aspects.[5]

The aim of our research was (1) to provide a comparative analysis of NHAs recommendations issued by 8 different European countries, (2) to analyze if there was any relationship between the type of the European Medicines Agency (EMA) approval (conditional approval or under exceptional conditions vs standard approval) that could affect the reimbursement decision, and (3) to provide insights of the key considerations that played a role in the NHA reimbursement recommendations.

Methods

An analysis of NHAs reports of authorized ATMPs in 8 European Union (EU) countries (EU8) has been conducted using the following approach:

Search Strategy

Data collection was primarily extracted from available NHAs reports, such as health technology assessments (HTAs) and other official national reports of the EU8, that is, Ireland, England/Wales, Scotland, The Netherlands, France, Germany, Spain, and Italy. The inclusion of countries was according to the largest European countries and HTA report availability written in a language understood by the researchers. The search was carried out until December 31, 2021. In addition, a search for related publications was performed for pricing (ie, gray literature: open search and non–peer review journals).

Eligibility Criteria

Only products classified as ATMPs according to the EMA criteria[6,7] and authorized under centralized procedure in the EU have been considered for the analysis.

Data Extraction and Collected Variables

The authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA) to collect information. A review of NHAs reports of approved ATMPs published by national bodies in each country was conducted. The national bodies and the type of HTA reports analyzed for each country are reported in Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014.

For each ATMP/indication and NHA body, the following variables were collected: type of EMA approval, reimbursement recommendation, financing conditions, drug comparator used for the cost-effectiveness analysis and incremental cost-effectiveness ratio (ICER), reported price of the product (notified price or applicants requested price), date of publication of technology appraisal guidance, and the date of recommendation implementation. Only reports describing the initial assessments were included, excluding resubmissions. For the ICERs, the base case accepted by the agency after corrections was chosen. Time from EMA approval to NHA recommendation in their appraisal reports and time from EMA approval to implementation (ie, product available to the patients) were analyzed.

It was assessed if there was any relationship between the type of EMA approval (conditional approval or under exceptional conditions vs standard approval) that could affect the reimbursement decision, given that less comprehensive data might be available.

The key considerations that played a role in or might have influenced the NHA reimbursement recommendation or final decision were collected for those products with an available NHA assessment report (in which these considerations could be extracted). After identification of all HTA reports of authorized ATMPs, considerations that had an influence on reimbursement were extracted—a consideration was defined as follows: "a value judgement of the HTA-body during the assessment." These key considerations were classified according to the 5 European Network for Health Technology Assessement HTA Core Model® (version 3) domains and the HTA Core Model for Rapid Relative Effectiveness Assessments domains (version 4.2).[8,9] A review was conducted for the published reports of approved ATMPs to compare the aforementioned variables of the ATMP assessments across the 8 NHA bodies. The items or considerations included in the NHAs reports that might have had an influence on the reimbursement final decision were classified according to the prespecified domains. In addition, these considerations were classified according to the ATMP type: gene therapies (chimeric antigen receptor T cell [CAR-T] products), gene therapies that consist of viral vector–delivered or cell-based therapies and cell- and tissue-engineered products. Data extraction and analysis were conducted by one author, and a second author validated it. Inconsistencies were discussed until consensus was reached.

Statistical Analysis

A descriptive statistical analysis was performed using means, median, and range (minimum and maximum). The relationship between the type of EMA approval and the reimbursement decision was assessed by a chi-square statistic test with Yates correction. A P value $< .05$ was considered statistically significant.

Results

The analyzed products and the type of approval granted by the EMA are listed in Table 1. A total of 19 approved ATMPs were included for 20 indications, 7 of those were authorized under conditional or exceptional circumstances. In addition, 7 ATMPs were withdrawn from the market. A total of 76 NHAs appraisal reports or summaries among the analyzed countries were available and analyzed.

Recommendations of Reimbursement and Type of Reimbursement Schemes

The majority of the ATMPs were initially reimbursed in most EU8, except in the case of Ireland (Table 2). Germany reimbursed all the 13 ATMPs for 14 indications, as well as The Netherlands (6 ATMPs were reimbursed except for 1 indication of 1 product). England and Wales agreed for the reimbursement of 11 out of 12 assessed ATMPs, similar to France with 10 out of 14 and Italy with 7 out of 8 products. Ireland did not reimburse any of the 5 assessed ATMPs at an initial stage but did it later after reassessment with CAR-T products.

England and Wales, Scotland, The Netherlands, France, and Spain narrowed the authorized indication for the reimbursement of some ATMPs. Germany did not restrict any ATMP to specific conditions within the authorized indication.

Most countries established some types of reimbursement schemes, but the specific type of schemes is divergent among the EU8. Managed entry agreements (MEAs) or patient access schemes are regularly used in Scotland and England, determining specific conditions for reimbursement, usually in a confidential manner. Payment based on outcomes are more frequently used in The Netherlands, Spain, and Italy where financing is linked to the achievement of certain clinical outcomes. This risk-sharing reimbursement approach might allow discounts and rebates.

The type of EMA approval did not have an influence on the reimbursement decision (chi-square 0.4742; $P = .492$).

Determination of a Product's Added Therapeutic Value

The determination of a product's added therapeutic value (ATV) has different implications in terms of recommendations, reimbursement negotiations, and granting the drug innovativeness status. In Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014, these implications are further discussed by country. There is not a harmonized or defined standard for ATV classification, and the assessment criteria is different in each country. In France, Italy, and Germany, the ATV is assessed

Table 1. Analyzed ATMP approved in the European Union.

Type of ATMP	Brand name	INN	Pharmacotherapeutic group	Orphan drug designation	Type of authorization and current status
GTMP	Glybera®	Alipogen tiparvovec	Lipid modifying agents	Yes	Exceptional circumstances. Withdrawn
	Imlygic®	Talimogene laherparepvec	Antineoplastic agent	No	Standard
	Kymriah® (DLBCL)	Tisagenlecleucel	Antineoplastic agent	Yes	Standard
	Kymriah® (ALL)	Tisagenlecleucel	Antineoplastic agent	Yes	Standard
	Yescarta®	Axicabtagene ciloleucel	Antineoplastic agent	Yes	Standard
	Tecartus®	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	Antineoplastic agent	Yes	Conditional
	Strimvelis®	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Immunostimulants	Yes	Standard
	Luxturna®	Voretigene neparvovec	Ophthalmologicals	Yes	Standard
	Zynteglo®	Betibeglogene autotemcel	Other hematological agents	Yes	Conditional. Withdrawn
	Zolgensma®	Onasemnogene abeparvovec	Other drugs for disorders of the musculoskeletal system	Yes	Conditional
	Libmeldy®	Atidarsagene autotemcel	Other nervous system drugs	Yes	Standard
	Abecma®	Idecabtagene vicleucel	Antineoplastic agent	Yes	Conditional
	Skysona®	Elivaldogene autotemcel	Other nervous system drugs	Yes	Standard. Withdrawn
SCTMP	Provenge®	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	Other immunostimulants	No	Standard. Withdrawn
	Zalmoxis®	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	Antineoplastic agents	Yes	Conditional. Withdrawn
	Alofisel®	Darvadstrocel	Immunosuppressants	Yes	Standard
TEP	Chondrocelect®	Characterized viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	Other drugs for disorders of the musculoskeletal system	No	Standard. Withdrawn
	MACI®	Matrix-applied characterized autologous cultured chondrocytes	Other drugs for disorders of the musculoskeletal system	No	Standard. Withdrawn
	Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system	No	Standard
	Holoclar®	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals	Yes	Conditional

ADA indicates adenosine deaminase; ALL, B-cell acute lymphoblastic leukemia; ATMP, advanced therapy medicinal product; cDNA, complementary DNA; DLBCL, diffuse large B-cell lymphoma; GTMP, gene therapy medicinal product; INN, international nonproprietary name; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.

Table 2. Overview of initial reimbursement recommendations and financing conditions of approved advanced therapy medicinal products in the Europe Union (December 2021).

Product/indication		Scotland	Ireland	England and Wales	The Netherlands	Italy	Spain	France	Germany
GTMP	Glybera®							‡	*
	Imlygic®			MEA†			‡		*
	Kymriah® (DLBCL)	MEA/OEP*	*ODM§	MEA*	‡	PBO*	PBO†	*	*
	Kymriah® (ALL)	MEA/OEP*	*ODM§	MEA*	OEP*	PBO*	PBO†	*	*
	Yescarta®	MEA/OEP*	‡	MEA*	MEA*	PBO*	PBO†	*	*
	Tecartus®	MEA/OEP*		MEA*				*	*
	Strimvelis®			*		PBO*			
	Luxturna®	MEA/OEP†	‡	MEA*	PBO/OEP*	*	PBO*	*	*
	Zynteglo®				PBO/OEP*			†	*
	Zolgensma®	MEA/OEP†	‡	MEA†	PBO†	†		†	*
	Libmeldy®							†	*
	Abecma®								
SCTMP	Provenge®								*
	Zalmoxis®					*		‡	*
	Alofisel®	OEP‡	‡	‡		‡	PBO†	†	*
TEP	Chondrocelect®			†	†			‡	
	MACI®			MEA†					
	Spherox®			†				‡	
	Holoclar®	OEP†		†		PBO*	‡	†	*
Available reports/ indication	20	8	6	13	7	9	7	14	14

ALL indicates B-cell acute lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; GTMP, gene therapy medicinal product; MEA, managed entry agreement; ODM, Oncology Drug Management System; OEP, ultraorphan or end-of-life process; PBO, payment based on outcomes; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.
*Positive recommendation.
†Positive recommendation with restricted indication.
‡Negative recommendation.
§Initial negative recommendation and finally, reimbursement following confidential price negotiations on July 2021.

as a separate parameter according to several ranks and scales, whereas in Scotland, Ireland, and Spain, there is no publicly defined ATV classification, and it seems to be a part of their clinical effectiveness assessment. The Netherlands uses a binary categorical classification system, classifying whether a product has ATV or not, which is called "established medical science and medical practice."[10]

Table 3 compares the ATV assigned per product in France, Italy, Germany, and The Netherlands. In Italy, of the 6 indications (5 ATMPs) in which innovativeness was assessed, 4 indications obtained the innovative status, and 2 were denied. For those products, the ATV was graded as "important" for 4 indications, as "moderate" for 1, and as "low" for 1. In Germany, of the 14 indications (13 ATMPs) approved, 3 were classified as having the "added benefit not proven," 7 were classified as "hint for a non-quantifiable additional benefit" because the scientific data does not permit quantification, 1 product was classified as "hint for a considerable additional benefit," and 2 products were not subject to the scope of the benefit assessment. From the 7 available HTA reports in The Netherlands, 5 assessed indications were considered "substitutable" or with similar therapeutic value, 1 was considered to be equal as SoC, and 1 was concluded to provide insufficient evidence of its intended effects. In France, most ATMPs had a minor or moderate ATV. Overall, there is a benefit found in these drugs, but there are differences in how the magnitude of this benefit is considered among countries (Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014).

Special Funding Process That Affects Reimbursement Decision

Most countries have special funding processes regarding the reimbursement decisions related to orphan drugs, drugs that are targeted to treat patients in their last months of life (also called end-of-life medicine), the disease severity, or to cover an unmet medical need. In Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014, the considerations for special funding processes are further discussed by country.

Of the 7 ATMPs assessed in Scotland, all were submitted under the orphan or end-of-life processes. In England and Wales, 3 ATMPs (Kymriah® in diffuse large B-cell lymphoma indication, Yescarta®, and Tecartus®) met the criteria for life-extending treatments, but Kymriah® in acute lymphocytic leukemia indication did not. From 13 analyzed drugs, 4 were assessed under the Highly Specialized Technology procedure (Strimvelis®, Luxturna®, Zolgensma®, and Libmeldy®). In The Netherlands, 3 ATMPs were reported to have an orphan drug agreement. In Germany, 3 of the 7 analyzed and approved drugs obtained an orphan drug agreement to guarantee patient access.

Table 3. Product ATV and innovativeness status.

Product/indication		Italy	France	Germany	The Netherlands
GTMP	Glybera®		Insufficient clinical benefit	No added benefit proven	
	Imlygic®			No added benefit proven	
	Kymriah® (DLBCL)	INV/important added value	CAV IV: minor added value	Nonquantifiable added benefit	Does not comply with established medical science and medical practice: insufficient evidence of the intended effects*
	Kymriah® (ALL)	INV/ important added value	CAV III: moderate added value	Nonquantifiable added benefit	Meets the statutory criterion of "established medical science and medical practice"
	Yescarta®	INV/important added value	CAV III: moderate added value	Nonquantifiable added benefit	Meets the statutory criterion of "established medical science and medical practice"
	Tecartus®		CAV III: moderate added value	Nonquantifiable added benefit	
	Luxturna®	INV/important added value	CAV II: substantial added value	Hint for a considerable additional benefit	Meets the "current state of science and practice" criterion, but with great uncertainties on long-term effects and the cost-effectiveness
	Zynteglo®		CAV III: moderate added value	Nonquantifiable added benefit	Meets the "current state of science and practice" criterion, but with great uncertainties on long-term effects and the cost-effectiveness
	Zolgensma®	INV/important added value	CAV III: moderate added value	No added benefit proven	Meets the "current state of science and practice" criterion but the scientific data does not permit quantification of added value with the comparator
	Libmeldy®		CAV III: moderate added value	Nonquantifiable added benefit	
SCTMP	Zalmoxis®	Non-INV/moderate added value	-	Nonquantifiable added benefit	
	Provenge®			Nonquantifiable added benefit	
	Alofisel®	Non-INV/minor added value	CAV IV: minor added value	Nonquantifiable added benefit	
TEP	Holoclar®	Unknown	CAV IV: minor added value	†	
	ChondroCelect®		Insufficient clinical benefit		Therapeutic value equal to comparator

Italy: the 5 categories of ATV are as follows: maximum (the drug has proven larger efficacy than any possible existing alternatives to the point of cure or significantly alter its natural history), important (the drug has a proven larger efficacy measured on clinically relevant endpoints, decreases the risk of invalidating or fatal complications, avoids highly dangerous clinical procedures or has more favorable risk/benefit ratio than any available alternatives), moderate (the drug has a larger efficacy than any available alternatives, but it is only moderate or only proven in some subsets of patients, with limited impact on the quality of life), poor (the drug has either a limited improvement of efficacy or has been proven on endpoints which are not clinically relevant, minor advantages, eg, more acceptable administration route), absent (the drug has no relevant benefit when compared with other available treatments).
France: the CAV categories are: major (CAV level I), substantial (CAV level II), moderate (CAV level III), minor (CAV level IV) or no improvement (CAV level V), with the latter level corresponding to no therapeutic progress.
Germany: the 6 categories of ATV are as follows: major, considerable, minor, and nonquantifiable added benefit; no added benefit proven; the benefit of the drug under assessment is less than the benefit of the appropriate comparator therapy.
The Netherlands: "established medical science and medical practice": product leads to relevant (added) value for the patient in comparison with the standard or usual treatment; "net benefit" of the intervention being assessed is a relevant and sufficiently large benefit in comparison with all existing care.
ALL indicates B-cell acute lymphocytic leukemia; ATV, added therapeutic value; CAV, clinical added value; DLBCL, diffuse large B-cell lymphoma; GTMP, gene therapy medicinal product; INV, innovative status granted; Non-INV, innovative status not granted; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.
*In a reassessment performed in January 2022, it was concluded that Kymriah meets the legal criterion of "established medical science and medical practice" in patients with r/r DLBCL.
†Ex vivo expanded autologous human corneal epithelial cells containing stem cells are therefore not included in the scope of the benefit assessment according to Section 35a Social Code Book V.

Table 4. Time (months) from EC approval to the NHA recommendation and product market access.

Type of ATMPs		EC approval date	HTA recommendation	HTA recommendation	Implementation	HTA recommendation	Implementation
			Scotland	Ireland		England and Wales	
GTMP	Glybera®	October 25, 2012					
	Imlygic®	December 16, 2015	16	2		9	12
	Strimvelis®	May 26, 2016				20	23
	Kymriah® (DLBCL)	August 22, 2018	12	12	34‡	6	8
	Kymriah® (ALL)	August 22, 2018	5	18	34‡	3	5
	Yescarta®	August 23, 2018	13			5	7
	Luxturna®	November 22, 2018	14	21		10	13
	Zynteglo®	May 29, 2019					
	Tecartus®	14-December 14, 2020	7			2	4
	Zolgensma®	May 18, 2020	9	10		13	16
	Libmeldy®	December 17,2020					
SCTMP	Provenge®	September 6, 2013					
	Zalmoxis®	August 18, 2016					
	Alofisel®	March 23, 2018	15	18		9	
TEP	Holoclar®	February 17, 2015	66			30	33
	Spherox®	July 10, 2017				7	10
	Median, months		13	15	34	9	11
	Range Max, months		66	21	-	30	33
	Range Min, months		5	2	-	2	4

Note. NHA recommendation: time (months) from EC approval to the date of publication of technology appraisal recommendation. Implementation: time (months) from EC approval to date of implementation of NHA recommendation. When information is not publicly available, there is a blank gap. There is no information published for Abecma® and Skysona® as of December 31, 2021. MACI® and Holoclar® were evaluated via the medical procedure in Germany and not as a medicine, which undergoes the benefit assessment procedure.

ALL indicates B-cell acute lymphocytic leukemia; ANSM, National Agency for the Safety of Medicines and Health Products; ATU, Authorization of Use; DLBCL, diffuse large B-cell lymphoma; EC, European Commission; GTMP, gene therapy medicinal product; HTA, Health Technology Assessment; Max, maximum; Min, minimum; NHA, National Health Authority; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.

*Cohort temporary ATU granted in France.

†Received nominative ATUs in France from June 2019 and a cohort ATU granted by the ANSM on May 15, 2020 in the marketing authorization indication.

‡Finally, reimbursement following confidential price negotiations on July 2021.

§Early access scheme.

Time to Market Access

The time from EC approval to the national NHA recommendation on financing decision and product market access is summarized in Table 4. Overall, the median time to NHA recommendation for the EU8 is in the range of 9 to 17 months, the time to implementation being the same as the time to NHA recommendation in Germany and +2 or +3 months in England. For the other countries that were analyzed, the time to implementation could not be determined due to limited data.

In France, products can be reimbursed before central authorization via the Temporary Authorization of Use (ATU) on a named patient basis (nominal ATU) or for all patients for a given indication (cohort ATU).[11,12] From 10 analyzed products in France, 4 received ATU; 3 products received cohort ATU (Kymriah®, Yescarta®, and Luxturna®) and 1 received nominative ATU and a cohort ATU later in the marketing authorization indication (Zolgensma®). This allowed that once the Committee for Medicinal Products for Human Use opinion was positive the patients could already have access to the medicine without the need of waiting for EC Decision and the HTA full evaluation period. During the ATU validity, the company can set a free price before the negotiation, but subsequently, the ASMR category will be a driver for price negotiation. The data generated during this period are used in addition to the clinical data from pivotal trials to inform the subsequent HTA and reimbursement determination at the time of marketing authorisation.[12,13]

In Scotland, the "interim acceptance decision" was introduced in 2018, which also allows that the SMC should have the option to accept a medicine for use, which is subject to ongoing evaluation and future reassessment for those drugs with a conditional marketing authorization by the EMA or Medicines and Healthcare

Table 4. Continued

HTA recommendation	Implementation	HTA recommendation	HTA recommendation	Implementation	HTA recommendation	HTA recommendation	Implementation
The Netherlands		Italy	Spain		France	Germany	
						27	30
			26			11	11
6		15	4	4	6*	24	24
3		15	4	4	6*	24	24
6	20	21	10	10	6*	8	8
14			29	29	6*	10	10
25					9	11	11
					4	7	8
11		13			7†	17	17
					10§	10	10
						18	18
					30	22	22
			17	17	11	7	7
			18		23	-	-
					35		
8.5	20	15	17	10	9	11	11
25	-	21	29	29	35	27	30
3	-	13	4	4	4	7	7

products Regulatory Agency early access to medicines scheme or innovative licensing and access pathway.[14] Tecartus® and Holoclar® were accepted in the interim for use in National Healht Sevice Scotland.

Comparators Used for the Cost-Effectiveness Analysis, Notified Prices, and ICER

The ICER thresholds varied depending on the country (Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014). Appendix Table 1 in Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014 shows the comparators used to determine the cost-effectiveness analysis of the analyzed ATMPs. The comparators used in the analyzed countries consist of similar SoC or best supportive care. This information was not available for Spain for any product. Most of the therapies are above the set thresholds ranging from €45 000 per quality-adjusted life-year (QALY) to less than €100 000 per QALY (Table 5). The estimated ICER for each product in each country and between countries reveals high variability. The notified prices are aligned across all the EU8 (Table 6).

Key Considerations That Influenced the Reimbursement Decision

The key considerations that might have influenced the reimbursement decision are summarized in Appendix Table 2 in Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014 according to ATMP product. A total of 33 reports were analyzed from Scotland, Ireland, England, and The Netherlands NHA bodies: 3 CAR-Ts for 4 indications (14 reports in total), 5 viral vector gene therapies (13 reports in total), and 3 cell therapies (6 reports in total). Several factors within European Network for Health Technology Assessement domains were considered (Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014).

Discussion

Although the majority of the ATMPs were reimbursed in most EU8, the decisions are heterogeneous among these European countries based on how HTA agencies interpret evidence and the associated uncertainties. Whereas most of the approved ATMPs were reimbursed in Germany, none of them were initially financed in Ireland, mainly because of the high uncertainty of efficacy evaluation. Although Germany had the highest approval rate, this was mostly achieved with an unquantifiable benefit. Nevertheless, this is not only the case for ATMP and is common and depends on how the appraisal is conducted. For other countries, there is a substantial tendency to issue a positive recommendation but restricting the approved indication. The type of EMA approval does not seem to have an influence on the

Table 5. Reported ICER for the approved ATMPs in the European Union

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	France
Imlygic®			• £23 900/QALY vs dacarbazine • £24 100/QALY vs BSC			
Kymriah® (ALL)	£25 238/QALY vs salvage chemotherapy	• €75 748/QALY-€116 506/QALY vs blinatumomab • €75 990/QALY-€107 163/QALY vs FLA-IDA	• £44 299/QALY vs blinatumomab • £74 322 per QALY vs salvage chemotherapy	Estimated added costs vs blinatumomab ranging €1.8-€2.1 million and €1.8 million allogenic bone marrow transplant*	€32 543 80/QALY vs salvage chemotherapy	• €90 029/QALY vs salvage chemotherapy as reference and blinatumomab over a lifetime horizon • €189 822/QALY vs rescue chemotherapy baseline and blinatumomab over a 10-year time horizon
Kymriah® (DLBCL)	• £44 330-48 116/QALY vs [R-] Gem-Ox; • £44 151-47 903/QALY vs [R-] GDP	• €1 035 700/QALY vs SCHOLAR-1 • €734 534/QALY vs CORAL extension studies	£42 991-£55 403/QALY (with the discount agreed)		€60 680 63/QALY vs salvage chemotherapy	€294 381/QALY over 10 years
Yescarta®	£49 136/QALY	€87 957/QALY	£50 000/QALY vs salvage chemotherapy	€46 048/QALY-€600 262/QALY vs SoC*	€54 699/QALY vs BSC	€97 015/QALY (€84 766/QALY before the technical exchange)
Tecartus®	£49 711/QALY vs SoC		£46 898-£72 920/QALY			€111 649/QALY
Strimvelis®			£494 255-£170 668 incremental costs when compared with an HSCT from a MUD and a haploidentical donor respectively			
Luxturna®	£89 871/QALY vs BSC	€189 037/QALY vs BSC (a discount rate of 4% on costs and outcomes is applied)	£60 908-£86 118/QALY (do not include the company's commercial arrangement)			€191 811/QALY vs BSC over a time horizon of 85 years (lifetime)
Zynteglo®				€90 000 per QALY		€ 151 003/QALY vs better supportive care (transfusions + iron chelators), a price of −15% results in an RDCR of 106 175 €/QALY
Zolgensma®	£59 996-£74 000/QALY vs BSC	€298 469/QALY vs Nusinersen €387 717/QALY vs BSC	ICERs cannot be reported	€263 389/QALY vs Nusinersen	€51 690/QALY vs Nusinersen	from €576 000/QALY-€2.6 million/QALY over a time horizon of 10 years and €212 226/QALY-€1.5 million/QALY over a lifetime time horizon depending on the data source chosen
Alofisel®	£20 930/QALY darvastrocel vs surgical examination ± seton placement plus curettage	€109 058-€248 548/QALY	£23 176/QALY			
Chondrocelect®			£14 000/QALY			

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Table 5. Continued

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	France
Spherox®			• £4360/QALY vs microfracture • Lower than £20 000/QALY vs BSC			
Holoclar®	£3483/QALY vs BSC		• £42 139/QALY vs conjunctival limbal allograft from a living related donor • £30 415/QALY vs keratolimbal allograft £6948/QALY vs BSC			

Note. ICER is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance. The indicated costs of the table are per patient and QALY gained.
ALL indicates B-cell acute lymphocytic leukemia; ATMP, advanced therapy medicinal product; BSC, best supportive care; DLBCL, diffuse large B-cell lymphoma; FLA-IDA, fludarabine, cytarabine and idarubicin; GDP, gross domestic product; HSCT, hematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; MUD, matched unrelated donor; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; RDCR, ratio différentiel coût-résultat; SoC, standard of care.
*No cost-effectiveness analysis was not carried out. For Yescarta®, comments on cost-utility analysis from NICE were considered. No economic analysis was performed; Information for Glyebra®, Libmeldy®, Abecma®, Provenge®, Zalmoxis®, and MACI® is not available.

reimbursement decision, probably because of the type of indications targeted, that is, rare, last lines of treatment (in which there is an unmet need), or serious conditions. Our results showed that the potential benefit of these therapies was acknowledged, but overall, the high degree of uncertainty associated with the magnitude of clinical efficacy and safety hampered the decision and made the evaluation complex. Some studies have confirmed that single-arm study, short-duration, and indirect comparison were reported as a major efficacy uncertainty, and it is suggested that the access to these therapies is lower in the EU than in the United States.[15] We found that considerations that might have influenced the decision could go beyond the 3 common core domains (clinical effectiveness, safety, and cost-effectiveness) and include items related to the "health problem and current use of technology" and "patient and social aspects" domains, because most therapies are targeting orphan or end-of-life conditions. Other studies have suggested that the incorporation of additional "social value judgements" (beyond clinical benefit assessment) and economic evaluations could help explain heterogeneity in coverage recommendations and decision making.[16] Budget impact, gross domestic product, involvement of patient advocacy groups, equity considerations, and different economic evaluations performed among European countries could also contribute to this heterogeneity.

In terms of the type of reimbursement scheme applied, the trends are divergent among the EU8—different in each country with different special funding processes but with an extended use of MEAs. It has been recognized that a single payment model is unlikely in the case of ATMPs.[17] The use of MEAs, which are mainly negotiated when there is uncertainty regarding the drug clinical benefit, allows the introduction of new products with potential benefit, but it is not seen as a solution to address high prices and uncertainties associated with the ATMPs.[18,19] The introduction of the 2 initial CAR-T products, Kymriah® and Yescarta®, constituted the first examples of national reimbursement schemes involving outcomes-based, staged payments for innovative therapies in Germany, Italy, and Spain.[12,13,20] Nevertheless, the implementation of these agreements is not always easy, because the burden of monitoring this process is challenging, and can differ among countries. Different agreements arise for the same treatment in different jurisdictions, making it challenging for the sponsor and inefficient in terms of sharing of outcomes data across jurisdictions, which could facilitate more robust evidence for reappraisal.[21] In those countries where payment by results are not used, a continuous reassessment could be an approach to manage the decision uncertainties associated with these therapies (eg, based on cohort data from a combination of follow-up from the pivotal trials and real-world evidence).[12,13] Broad principles for innovative payment models for high-cost innovative medicines have already been addressed by the EC.[22] On the industry side, a concrete list of recommendations has been proposed, which includes payment models that distribute costs over time.[23] It is still uncertain how, with the expansion of ATMPs to high-prevalent diseases, patients will have rapid access to innovation while keeping health systems financially sustainable. Value-based pricing methodologies are suggested to be an option to cope with the specific challenges of ATMPs.[24]

For the NHAs, the ATV of a new drug compared with the best available treatment options is one of the key points to make their recommendation on reimbursement. Although no major significant differences have been found when the ATV for approved ATMPs has been compared among countries, a comparable and unified criterion was not used. Other studies have reported low rates of agreement on the ATV of ATMP and non-ATMP drugs compared with the SoC among Germany, Italy, and France.[25,26] The main reasons for the inconsistency were found to be related to a different appreciation of the subgroup analysis of efficacy data, the appropriateness of comparators, the surrogate endpoints, methodological differences, and the benefit/risk criteria that were used.[26] A study has already been performed with the aim to investigate the feasibility of a harmonized EU approach concerning the assessment of the ATV of medicines in the EU.[27] In this report, it is suggested that the ATV should be measured on an ordinal scale, as well as by a multidisciplinary team of trained experts independent from the committees in charge of determining the reimbursement and product price. A harmonized definition of ATV would clarify the expected benefits of a new drug, set rewards for higher therapeutic added value and promote the innovation.[27] In contrast, it is also under discussion how the ATV of ATMPs, in particular, should be assessed.

Table 6. Notified prices reported for the approved ATMPs in the European Union.

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	Spain	Germany
Glybera®							€1 321 139 (26 vials per patient)
Imlygic®			£1670 per vial				Annual therapy costs €72 287 80-€289 151 20
Kymriah® (ALL)	£282 000 per infusion	Total cost including rebate is €301 762; VAT is not applicable	£282 000 per infusion (company submission). Commercial arrangement	The total cost of €320 000 per patient and per treatment	€320 000 (excluding VAT)	€320 000 (excluding VAT)	Annual therapy costs €282 419 28-€283 244 95
Kymriah® (DLBCL)	£282 000 per infusion	Total cost including rebate is €301 762; VAT is not applicable	£282 000 per infusion (company submission). Commercial arrangement		€320 000 (excluding VAT)	€327 000 (excluding VAT)	Annual therapy costs per patient €283 062 13-€291 815 14
Yescarta®	£282 451 per infusion	The total cost including rebate and VAT is €384 225	Price submitted as commercial in confidence	€327 000 per infusion (including conditioning chemotherapy)	€327 000 (excluding VAT)		2 single infusion bag €389 130
Tecartus®	£316 118 per infusion		Price submitted as commercial in confidence				1 single infusion bag €360 000
Strimvelis®			£505 000 (excluding VAT; company's evidence submission)		€594 000	€355 000 per vial	
Luxturna®	£658 946 (in each eye)	€690 000 (for 2 single-use packs, 1 for each eye)	£613 410 per patient (excluding VAT; company submission); commercial arrangement	€690 000 (for 2 single-use packs, 1 for each eye)			€321 000 (for both eyes)
Zynteglo®							€1 929 926 88-€1 936 134 22
Zolgensma®	£1 795 000 single infusion	Price to wholesaler €1 945 000, €2 285 375 (including 23% VAT)	£1 795 000 (excluding VAT; company submission). Commercial arrangement		€2 155 124 65 (excluding VAT)	€1 945 000	€2 314 550
Libmeldy®			£2 875 000 (excluding VAT; company submission)				€2 875 000
Provenge®							Annual therapy costs per €79 952 58
Zalmoxis®					€149 000	€60 000	Annual therapy costs per patient: €189 474 78-€757 899 12
Alofisel®		The cost per patient per year to the HSE (incorporating VAT and mandatory 5.5% rebate) is €70 500	£13 500 per vial. One course of treatment (4 vials) costs £54 000 (company submission). Commercial arrangement				€71 400 00
Chondrocelect®			£16 000 (company submission)				
MACI®			£16 226 per implant (price excluding VAT). Negotiated discounts				

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Table 6. Continued

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	Spain	Germany
Spherox®			£10 000 per culture per patient, including cell costs and transportation				
Holoclar®	£80 000 (1 treatment per limbal stem cell transplant)		£80 000 excluding VAT for 1 eye. Commercial arrangement		€95 000		

Note. No information for Abecma® is available yet.
ALL indicates B-cell acute lymphocytic leukemia; ATMP, advanced therapy medicinal product; DLBCL, diffuse large B-cell lymphoma; HSE, health service executive; VAT, value-added tax.

The challenges of the standard value and price assessment methods in the evaluation of ATMPs have already been analyzed, and new elements to define their value have been proposed. These new elements are more focused on societal perspective and not only on comparative clinical benefit and economical aspects, for example, value of hope, real option value, and scientific spillovers.[28,49] It has been reported that the assessments of additional values beyond QALY are often based on "deliberative decision making," which is criticized for the lack of a clear framework and transparency, as well as potential risks of double counting of additional values that are already included as part of HTA reports.[29] It is important to mention that in January 2018, the EC proposed a new regulation with the aim to promote more alignment in terms of HTA assessments, which was approved in December 2021. This regulation aims to replace the current system of cooperation between Member States on HTAs with a permanent framework for joint work, allowing a harmonized approach to clinical assessment of new medicines across EU Member States. With this new regulation that will be mandatory from 2025, transparency and more alignment in terms of pricing is also foreseen. Above all, it is fairly defined in a consistent way among the EU Member States to reflect the added value that the product can bring to patients.[30]

Drugs to treat orphan conditions, end-of-life medicines, and the disease severity and unmet medical needs are factors that have an influence in terms of a higher price, which is the critical feature of ATMPs that restrain the market access. It is generally recognized that drugs in these categories are unlikely to meet the preexisting cost-effectiveness threshold,[31] as well as a higher degree of uncertainty in evidence and assessment outcomes being accepted.[32] These type of applications are increasing access to drugs for end-of-life and rare conditions in Scotland, whereas they might not otherwise have been accepted.[33] It was also suggested that, in England, medicines for rare diseases not evaluated under the Highly Specialized Technology framework or with an appropriate modifier in the appraisal process are subject to disadvantages.[34] Cost-effectiveness analysis and ICER are variable among EU8, because most of ATMPs are above ICER thresholds set by the different countries, with a notified price range comprising between €2 00 000 and €2 million. Moreover, concerns in addition to the price are the additional costs of treating and managing these patients, which are the clinical infrastructure and skills of the clinical staff. The pre-evaluation of the organizational impact of ATMPs and the need for healthcare centers with the necessary resources are suggested requirements to be adopted in preparation for the launch and delivery of these therapies.[12,35] Gene therapies for orphan hereditary diseases comprise a unique group of products, usually administered at an early age and expected to last for the patient's entire life. The economic burden at long-term of these type of diseases with the current SoC might be underestimated and some studies suggest that efforts are needed to reduce costs through improved drugs.[36] Similar analyses have been performed with CAR-T products.[37] For this group of products, these increased ICERs and prices have been justified and the "willingness to pay" levels were exceeded on the assumption of improving long-term clinical outcomes and patient and caregiver quality of life. With these type of drugs, long-term payment with risk-sharing models and a price without the premium addition have been proposed to help with the affordability, patient access, and the given uncertainty on effect durability.[38] The partnership and joint assessments across several countries to make the medicines more accessible to patients have already been applied for some approved ATMPs, as was the case of Zolgensma® and Zynteglo® through the Beneluxa Initiative,[39,40] which led to a successful reimbursement recommendation and an aligned agreement on the price. Other cross-country collaborations aim to negotiate affordable and sustainable prices for new and innovative drugs.[41] In contrast, it should be noted that the gross domestic product, as well as the purchasing power of the population is not homogeneous among the different European countries. Therefore, it would also be necessary to adjust the prices for each country according to its gross domestic product.[42]

Additionally, the lack of transparency of the information on the NHA decision-making process and pricing (because the "real" prices are often unknown because of agreed confidential discounts) has been extensively discussed. The need for a more harmonized, systematic, and reproducible assessment process has already been discussed at the EC level.[43] Transparency and more alignment in terms of pricing is also foreseen, and above all it is fairly defined in a consistent way among the EU Member States to reflect the added value that the product can bring to patients.

The limitation of this study is the small sample size given the limited number of ATMPs approved. In addition, for the latest approved products, the public reports are not yet available given that the evaluations are still ongoing, which also reduces the sample size. Although 8 EU countries were evaluated, the lack of publicly available information and the lack of transparency for some countries led to believe that the study could not cover these 8 EU countries for some of the analyzed points. The conclusions cannot be generalized to other than the EU countries analyzed. The weight of each consideration that influenced the reimbursement decision could not be assigned for each domain, given that is not publicly available.

To sum up, transparent, harmonized, and systematic assessments of ATMPs across the EU NHAs is needed. Robust evidence on the clinical efficacy and safety of ATMPs and the reduction of their costs are key elements for their financing and reimbursement.

Supplemental Material

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