Identifying current ATMP market access challenges and strategies in France, Germany, Italy and Spain

HTA256

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INTRODUCTION

- The European Medicines Agency (EMA) defines advanced therapy medicinal products (ATMPs) as gene, somatic-cell and tissue-engineered therapies.[1] The first ATMP product approved in the European Union (EU) came in 2009 with the authorisation of ChondroCelect®[2]
- ATMPs offer groundbreaking new opportunities for the treatment of disease and injury. Many ATMPs currently approved in the EU also have an orphan drug designation
- Developing and commercialising ATMPs can be challenging. ATMPs have complex manufacturing processes resulting in a high cost of goods. In many instances, it is not possible to perform double-blinded clinical trials. Most available ATMPs are classified as orphan drugs developed for rare diseases or small patient segments with a high unmet need, with the most likely comparator being a placebo rather than a standard of care (SoC)
- Therefore, the EMA often bases its marketing approvals on small incomplete datasets
- ATMP use in limited patient numbers and high manufacturing costs restrict the companies' flexibility in their pricing strategies. At launch, payers are faced with high-cost products for a small patient population and limited data on clinical efficacy and safety, and patient value
- From the payer perspective, there will be uncertainty about long-term outcomes such as duration of effect and safety, no comparative data against SoC, and practical issues for use in the local clinical environment. All these aspects make payers hesitant to pick up high therapy costs
- **This study aimed to review the existing ATMPs approved in the EU and identify current challenges and potential solutions in attaining successful market access for ATMPs in France, Germany, Italy and Spain**

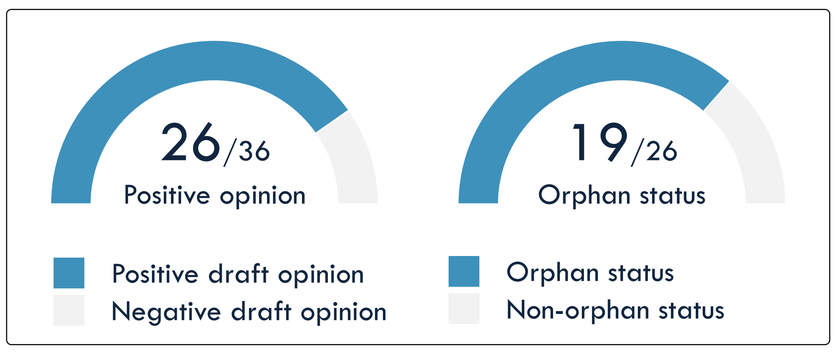
METHODS

- To answer the research question, we conducted a targeted review of ATMPs approved in the EU, country-specific market access legislation for the major four EU markets, health technology assessment (HTA) reports and literature
- The examined period ranged from 2009 to 2022
- Sources used included the EMA portal, national authority websites, published literature

RESULTS

- Between 2009 and 2022, the EMA received 36 submissions on ATMPs and issued 26 positive draft opinions, of which 19 were designated orphan drug status (Figure 1)

Figure 1. EMA assessment (2009–2022)



- Eight products were withdrawn from the market during this period (Table 1). Four manufacturers reported a lack of product reimbursement as a reason for withdrawal (ChondroCelect®, Provenge®, Zynteglo®, Skysona®). Other reasons for product withdrawal included limited patient populations, poor commercial performance due to too costly manufacturing processes and insufficient clinical data to support product benefit

Table 1. Reason for ATMP withdrawal

ATMP	Reason for withdrawal
ChondroCelect®	Poor commercial performance and lack of reimbursement in EU countries[3]
Glybera®	Ultra-rarity of the disease (1 in a million), high cost of therapy [over 1 million euro per patient] and large maintenance costs, because of the need to monitor patients over a long period of time[4]
Maci®	Poor commercial performance, administered via costly two-stage surgical procedures; one for tissue harvest and another for implanting resulting cell products[3]
Provenge®	Poor commercial performance and lack of reimbursement in EU countries[5]
Roctavian®	Unable to provide the data needed to resolve a 'major objection' raised by the EMA's Committee for Advanced Therapies. After successfully reapplying with missing data, Roctavian has been available again since August 2022[6]
Skysona®	Company closed operations in Europe to focus on the USA, a retreat driven by the company's difficulties in winning agreement from European payers on reimbursement for its gene therapies[7]
Zalmoxis®	Unfavourable results reported from the post-approval phase III clinical trial, a requirement for conditional market access[8]
Zynteglo®	A high price tag of $1.8million for Zynteglo led to Germany presenting a counteroffer of $790,000. Zynteglo was withdrawn from the German market followed by a broader withdrawal from Europe. Manufacturing difficulties led to a delay in the launch of the drug[7]

ATMP, advanced therapy medicinal products; EMA, European Medicines Agency; EU, European Union

- ATMPs without an orphan designation would proceed through a standard reimbursement route in all countries in scope (Table 2). Such processes do not account for the nuances of ATMPs that can lead to constraints on trial design, evidence availability such as small patient numbers, single arm or non-randomised controlled studies, limited trial duration, and lack of established competitors

Table 2. Requirements in the EU4

	Country-specific requirements
France	Normal reimbursement route via the National Authority for Health (HAS)[9]
Germany	ATMPs with a positive opinion from the EMA are checked by the G-BA to determine whether they are a drug or treatment.[9] While drugs undergo early benefit assessment, treatments will be assessed depending on the setting (outpatient/ambulatory or inpatient)
Italy	ATMPs go through the national reimbursement route via AIFA.[9] Current ATMPs have compulsory discounts and managed entry agreements (outcomes-based reimbursement, budget caps).[10,11] They are likely to achieve innovation status for 36 months if quality of evidence was considered low/very low/moderate by AIFA[12]
Spain	ATMPs are assessed using the standard P&R route[9] and are further put through Valtermed, a registry system designed to collect real-world clinical data to reduce decision uncertainty.[11] ATMPs are typically reimbursed using outcomes-based, staged payments[11]

AIFA, Agenzia Italiana del Farmaco; ATMP, advanced therapy medicinal products; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de santé; Valtermed, Valor Terapéutico de los Medicamentos

- The main objections to reimbursement at the national level therefore include trial design and lack of available evidence due to small patient numbers, single-arm or non-randomised controlled studies, too short trial duration, and lack of established competitors.
- However, country-specific hurdles need to be considered (Table 3)

Table 3. Reimbursement challenges in the EU4

	Main reimbursement challenges
France	Achieving an improvement (amélioration du service médical rendu, ASMR) score of I–III without survival data versus the SoC using single-arm trial data[10]
Germany	ATMPs suffer additional restrictions, mandating their use in specialised centres only[13]
Italy	Assessment of the added value of ATMPs compared with existing therapies at national and regional levels[10]
Spain	Limited regional budgets are a hurdle to uptake of high-cost ATMPs[10]

ATMP, advanced therapy medicinal products; SoC, standard of care

DISCUSSION

- For ATMPs, the main reason for product withdrawal was the poor commercial performance coupled with the lack of reimbursement in the key European countries
- After obtaining the EMA licence, ATMP manufacturers are faced with country-specific market access routes based on different requirements, creating a situation in which especially small and mid-size companies struggle to plan for and address all needs
- High manufacturing costs, challenges during the upscaling of drug manufacturing, and complex procedures result in high prices that might not be acceptable to some systems
- While post-launch data collections can be longer-term, especially for gene therapies, and thus costly, they are also associated with a risk of yielding less favourable clinical results (shorter duration of effect, new side effects)
- ATMPs without an orphan designation will be assessed in the same way as regular drugs, not duly considering ATMP product specificities and limitations, creating a high hurdle for manufacturers

CONCLUSIONS

- Whilst orphan ATMPs have a higher likelihood of attaining reimbursement, the challenges surrounding ATMPs warrant harmonisation of frameworks across regulators and HTA agencies to streamline reimbursement
- Manufacturers can strengthen their market access strategy by seeking national scientific and payer advice as early as possible to align on ATMP evidence requirements, thereby building engagement strategies with stakeholders across the sector to support market access

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