Reimbursement challenges for ATMPs in EU5: Learnings from product withdrawals and implications for future development of innovative therapies

Acceptance code: HTA385

Viktor Danev[1], Gerdi Strydom[1], Anna McCormick[1], Stephen Hall[1], Inês Oliveira[1]

[1]Valid Insight (Part of the Bioscript Group), Macclesfield, Cheshire, UK

Introduction and objectives

Advanced therapy medicinal products (ATMPs) usually come to the market with high clinical uncertainty, due to their small trial patient populations, limited study duration, and suboptimal trial design.[1] This clinical uncertainty leads to economic concerns, and decision-making is quite challenging for payers in many instances. Additionally, the lack of direct comparative data against the standard of care (SoC) has resulted in reimbursement challenges for some of these ATMPs across Europe.[2]

The objective of this study was to analyse the pricing and reimbursement (P&R) status of all ATMPs approved by the European Medicines Agency (EMA) from 2009 to 2025, identify the main reasons for ATMP withdrawal from the European market, and determine the key implications for manufacturers in the future.

Methods

A targeted search on the EMA webpage was conducted to capture all licensed ATMPs from October 2009 to June 2025. EMA and health technology assessment (HTA) reports from the HTA agencies in EU4 and the UK were retrieved to analyse ATMP marketing authorisation and reimbursement status, HTA outcomes, and contractual agreements with public health insurers in EU5.

Press releases and company position statements were reviewed to identify reasons for ATMP discontinuations in Europe.

P&R insights were analysed to capture key learnings from prior ATMP discontinuations, draw conclusions and determine reimbursement implications for the manufacturers of ATMPs, who aim to launch their products in Europe.

Results

The EMA approved 29 ATMPs from 2009 to 2025. Of them, nine (31.0%) have withdrawn their marketing authorisation for different reasons **(Table 1)**. Four (44.5%) were discontinued due to a combination of commercial and reimbursement challenges, three (33.3%) due to commercial reasons alone, and the remaining two (22.2%) because of clinical concerns **(Figure 1)**.

Most of the withdrawn ATMPs were not evaluated by European HTA authorities or there is currently no published evidence of HTA assessments, implying that they did not achieve wide reimbursement across the EU5 markets **(Figure 2)**.

The French National Authority for Health (HAS) issued positive HTA decisions on Alofisel and Zynteglo, but refused to provide funding for MACI, Glybera, and Zalmoxis due to insufficient efficacy and safety data and lack of comparative data against standard of care.

The Federal Joint Committee (G-BA) in Germany evaluated five (55.6%) of these ATMPs and assigned a non-quantifiable added benefit to them. The main reasons for the inability to quantify their added benefit include uncertainty in trial design, small patient population trial samples, non-validated disease endpoints, and incomplete datasets.

The Italian Medicines Agency (AIFA) assessed only one of the withdrawn ATMPs (Zalmoxis) and granted it a Class H designation.

Table 1. **ATMPs which have been withdrawn from Europe (2009–2025)**

Brand name	Reason for Withdrawal
Chondrocelect	Commercial reasons with the lack of reimbursement in key European countries
Glybera	Low product uptake and no anticipated product demand in the future
MACI	Poor commercial performance
Provenge	Poor commercial performance and lack of reimbursement in the EU countries
Zalmoxis	Unfavourable results from a post-approval Phase III trial, a requirement for a conditional MA
Alofisel	Product's clinical benefit was no longer sufficient to justify its continued use in the EU
Zynteglo	Unsuccessful negotiations with payers in Germany pulled the product from German and EU market
Skysona	Reimbursement challenges with EU payers resulted in the manufacturer closing down operations in Europe
Beqvez / Durveqtix	Limited interest from patients and physicians toward haemophilia gene therapies

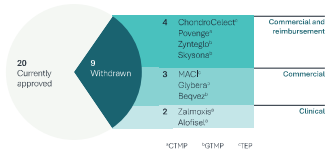
MA: marketing authorisation; EU: European Union

The Spanish Agency of Medicines and Medical Devices (AEMPS) in Spain issued a positive reimbursement decision for Chondrocelect, a neutral one (i.e., reimbursement restrictions in place) for Alofisel, and a negative decision for Zalmoxis due to high uncertainty in the clinical data, precluding clear positioning of the product in the healthcare system.

The National Institute for Health and Care Excellence (NICE) in the UK evaluated only three of the withdrawn ATMPs. MACI and Chondrocelect were initially granted a positive recommendation with restrictions in place; however, the marketing authorisation of both therapies was suspended over the course of the appraisal. Alofisel was issued a negative recommendation by NICE due to high uncertainty in the product's long-term benefits.

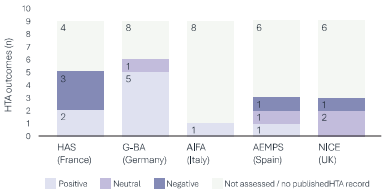
Analysis of the managed entry agreements (MEAs) in place for the nine withdrawn ATMPs reveals that none of them reached an innovative contracting agreement with the EU5 payers. Those ATMPs, which secured reimbursement in some of the EU5 markets, achieved this through traditional contracting agreements, such as confidential discounts (e.g., UK) or rebates (e.g., Germany).[4–9]

Figure 1: **ATMPs currently approved and withdrawn from the EMA (2009–2025) and reasons for these withdrawals**



CTMP: cell therapy medicinal product; GTMP: gene therapy medicinal product; TEP: tissue-engineered product

Figure 2. **HTA Outcomes of withdrawn ATMPs across EU5[5–9]**



Neutral HTA outcome indicates either reimbursement with certain restrictions in place or reimbursement on a case-by-case basis

All nine withdrawn ATMPs came to the market with a Phase III pivotal study **(Table 2)**. Six of them (66.7%), however, were assessed in a non-randomised and non-controlled trial. Four of the ATMPs (44.4%) were not directly compared to another product or placebo; instead, historical controls were used in their trials to compare treatment outcomes. Seven of the ATMPs (77.8%) used a surrogate primary endpoint, which is now always considered patient relevant by payers.

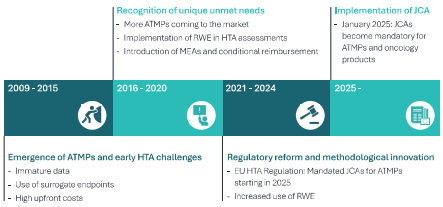
Until the mid-2010s ATMPs were mostly experimental and there were only a few products reaching regulatory approval **(Figure 3)**. Over the course of time, HTA bodies started to leverage real-world evidence (RWE) and implement managed entry agreements and innovative payment models, which explains the higher number of successful HTA assessments of ATMPs in the recent years. The implementation of the European Joint Clinical Assessment (JCA) in January 2025 marked a new milestone in the development of ATMPs, aiming to standardise the way all member states evaluate them for HTA.

Table 2. **Overview of trial characteristics of the withdrawn ATMPs from Europe[10]**

Brand name	Phase of pivotal study	Randomised controlled trial	Use of historical controls	Use of primary surrogate endpoints
Chondrocelect	Phase III	✓	✗	✓
Glybera	Phase III	✗	✓	✓
MACI	Phase III	✓	✗	✗
Provenge	Phase III	✓	✗	✗
Zalmoxis	Phase III	✗	✓	✓
Alofisel	Phase III	✗	✓	✓
Zynteglo	Phase III	✗	✗	✓
Skysona	Phase II/III	✗	✓	✓
Beqvez / Durveqtix	Phase III	✗	✗	✓

ATMP: advanced therapy medicinal product

Figure 3. **Evolution of HTA Frameworks in Europe**



ATMP: advanced therapy medicinal product; HTA: health technology assessment; JCA: joint clinical assessment; MEA: managed entry agreement; RWE: real-world evidence

Discussion and conclusion

This analysis reveals that achieving a marketing authorisation did not yield commercial success for nearly a third of the EMA-approved ATMPs, resulting in their withdrawal from the European market.

For most, the lack of commercial success was closely linked to reimbursement challenges with the EU5 public payers. HTA institutions did not evaluate many of the withdrawn ATMPs. Given that most of these ATMPs were the first of their kind to be launched in Europe, manufacturers faced the additional challenge of negotiating with payers, whose HTA frameworks were not tailored for innovative ATMPs associated with high uncertainty and price tags.

Most European HTA agencies adopt traditional HTA models, which are designed for chronic therapies and do not allow ATMPs to unveil their full value in HTA assessments. Over time, HTA bodies started to leverage real-world evidence (RWE) and implement managed entry agreements and innovative payment models, which explains the higher number of successful HTA assessments of ATMPs in recent years.

This analysis of the available evidence and trial design at the time of HTA submissions reveals that most of the withdrawn ATMPs had notable limitations in their evidence package. The pivotal trials of many of these ATMPs were non-randomised and non-controlled studies that used surrogate endpoints and/or historical controls, which add significant clinical uncertainty to HTA assessment and are criticised by payers. This, coupled with the traditional HTA models that were in place in the period 2010–2015 explains why the withdrawn ATMPs faced reimbursement challenges across the EU5 either due to negative HTA outcomes or because their manufacturers did not make a submission to the HTA authorities.

In contrast to the current ATMP reimbursement landscape, none of the withdrawn therapies leveraged an innovative contracting mechanism with public healthcare systems, highlighting the initial lack of payer flexibility in evaluating and funding such products.

Although the main purpose of JCA is to harmonise the P&R assessment for drugs across Europe, uncertainty remains as to how these products will be assessed. For example, manufacturers will only have 100 days from receiving the final population, intervention, comparator(s), and outcomes (PICO) scope to submit a JCA dossier, and the number of the requested PICOs is unknown.

Therefore, it will be key for manufacturers of ATMPs to align early on their evidence generation strategy to address these uncertainties. Additionally, they need to prepare robust economic evidence for the subsequent price negotiations at the national level. Lastly, but not least, the reimbursement landscape for ATMPs has undergone significant evolution over the past decade. Hence, manufacturers need to demonstrate contract flexibility and propose different options to payers to mitigate uncertainty and ensure a win-win situation for both parties, thereby guaranteeing success for their products.

References

1. Iglesias-Lopez et al. Molecular Therapy Methods & Clinical Development. 23:606–618.
2. Ten et al. Value in Health. 25(3):390–399.
3. Iglesias-López et al. Value in Health. 26(6):841–853.
4. Innovative Contracting for ATMPs in Europe (2023) Alliance for Regenerative Medicine. Available at: https://alliancerm.org/innovative-contracting-for-atmps-in-europe/
5. French National Authority for Health (HAS) (2025). Available at: https://www.has-sante.fr/
6. Federal Joint Committee (G-BA) (2025). Available at: https://www.g-ba.de/english/
7. Italian Medicines Agency (AIFA) (2025). Available at: https://www.aifa.gov.it/en/
8. The Spanish Agency of Medicines and Medical Devices (AEMPS) (2025). Available at: https://www.aemps.gob.es/?lang=en
9. National Institute for Health and Care Excellence (NICE) (2025). Available at: https://www.nice.org.uk/
10. ClinicalTrials.gov (2025). Available at: https://clinicaltrials.gov/

VALID INSIGHT®

PART OF THE BIOSCRIPT GROUP

validinsight.com

Valid Insight, Greenway House, Larkwood Way, Tytherington Business Park, Tytherington, Macclesfield, Cheshire, SK10 2XR

ISPOR, DD 11 2025©