Cell and Gene Therapy Access in the US and Europe

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HPR10

OBJECTIVE

Examine the pricing, reimbursement, and market access (PRMA) landscape for cell and gene therapies/Advanced therapy medicinal products (ATMPs) across the US and Europe (EU4/UK)

METHODS

- Reviewed all cell and gene therapies/ ATMPs **approved as of December 2022 (identified from FDA and EMA websites)** given the lengthy pricing and reimbursement (P&R) process timelines
- Included all cell and gene therapies/ ATMPs and **available in the US, EU4 (France, Germany, Italy, Spain), and UK as of December 31, 2023 in the analysis.**
  - Also noted products that have been withdrawn from market
- Analysed HTA, pricing, and reimbursement status based on the:
  - Data gathered from EMA, national Health Technology Assessment (HTA) agencies, and Pricing and Reimbursement (P&R) bodies
  - Sources for information provided in Table 1 below-

Table 1: Sources for HTA, pricing, reimbursement and time to market

Country	Sources
US	MediSpan, Fingertip formulary
France	Légifrance, Haute Autorité de Santé (HAS), Ministry of Health
Germany	Lauer Taxe, Gemeinsamer Bundesausschuss (G-BA)
Italy	Agenzia Italiana del Farmaco (AIFA), Gazzetta Ufficiale
Spain	Ministry of Health, Vademecum
UK	NHS DMD, National Institute for Health and Care Excellence (NICE)

RESULTS

- **A total of 33 cell and gene therapies/ATMPs were approved as of Dec 2022 and available as of Dec 2023**
  - US: 25 FDA-approved therapies (8 are cord blood products), 16 of which are currently marketed and reimbursed
  - Europe (EU4/UK): 17 EC-approved ATMPs currently available on the market (does not include therapies withdrawn)
  - Only 9 therapies available across both jurisdictions i.e., the US and Europe (EU4/UK)
- **Highest annual visible ex-factory prices for therapies reviewed:**
  - US: Hemgenix (etranacogene dezaparvovec-drlb) at $3.5M
    - Wholesale acquisition cost (WAC) and average selling price (ASP) are not significantly different for cell and gene therapies in the US
  - Europe: Upstaza (eladocagene exuparvove) at £3M (UK)
  - European net therapy cost following negotiation include ~10% to 45% reductions from the initial/visible ex-factory price
    - In Germany, the post-AMNOG negotiated price for Roctavian (valoctocogene roxaparvovec) is ~55% lower than the ex-factory price at launch
- **Of the 17 therapies approved in the EC, value judgments are not always positive or consistent across HTA agencies (Table 2)**
  - Only 3 therapies assigned a “considerable” or “major” added benefit rating in Germany with most assigned a “hint for a non-quantifiable” added benefit and 4 assigned “no-added benefit” in at least one patient sub-group
  - There seems to be some alignment between France and Italy with 7 therapies in France assigned ASMR II/III in at least one sub-group and 8 in Italy being recognized as innovative
- **Market access status of cell and gene therapies, ATMPs varies considerably across the six countries (Figure 1)**
  - US: All cell and gene therapies are generally covered under the medical benefit with restrictions typically based on disease severity, age, patient functioning and life expectancy
  - France: 76% of therapies are accessible, consisting of 41% reimbursed under the standard pathway and 35% available via the early access scheme (ATU/post-ATU/AAP)
  - Germany: Patients have access to all ATMPs with 65% having completed P&R procedures and 35% pending completion of the AMNOG procedure
  - UK: 65% of ATMPs recommended for reimbursement by NICE, 6% are undergoing NICE review and 29% are not reimbursed with no evidence submission or withdrawal of evidence submission from the manufacturer
  - Italy: 53% of ATMPs are reimbursed, all with patient registries and several with payment by results agreements
  - Spain: Only 47% of ATMPs have successfully completed P&R procedures with 29% denied reimbursement
- **Substantial difference in time to reimbursed market access noted (Figure 2)**
  - While in the US the average time to access is 4 weeks, in Europe the average ranges from 32 weeks in Germany and 91 weeks in Spain
- **Data above does NOT include ATMPs that have been withdrawn from markets^**
  - US: 2 therapies are no longer marketed
  - Europe: 7 therapies have been withdrawn post-approval for clinical/commercial reasons

Table 2: Health technology assessment (HTA) of 17 ATMPs in France, Germany and Italy (status as of Dec 31, 2023)

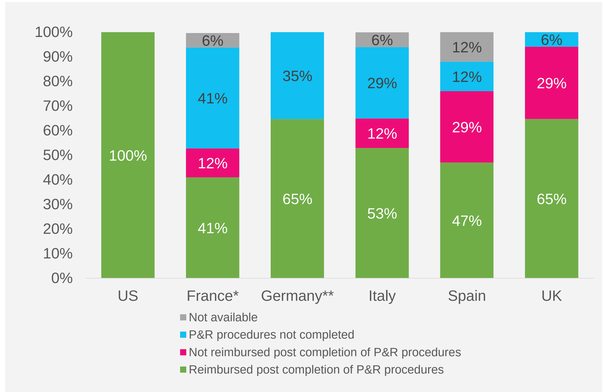
ATMPs	France (AMSR rating)	Germany (Benefit rating)	Italy (Innovation rating)
Abecma (idecabtagene vicleucel)	IV	Hint for a non-quantifiable added benefit	AIFA procedure ongoing
Alofisel (darvadstrocel)	IV	Non-quantifiable added benefit	Not Innovative
Breyanzi (lisocabtagene maraleucel)	III	Hint for a considerable added benefit/No added benefit	AIFA procedure ongoing
Carvykti (ciltacabtagene autoleucel)	V	Hint for a non-quantifiable added benefit	AIFA procedure ongoing
Ebvallo (tabelecleucel)	IV	Hint for a non-quantifiable added benefit	AIFA procedure ongoing
Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells)	IV	Not assessed by G-BA	Not Innovative
Imlygic (talimogene laherparepvec)	Not assessed by HAS	No added benefit	AIFA procedure terminated
Kymriah (tisagenlecleucel)	III (ALL)/ IV (DLBCL)/ V (FL)	Hint for a non-quantifiable added benefit	Formerly Innovative* (ALL & r/r DLBCL). Not innovative (FL)
Libmeldy (atidarsagene autotemcel)	III	Hint of a major additional benefit/ Hint for a non-quantifiable added benefit	Innovative
Luxturna (voretigene neparvovec)	II	Hint for a considerable added benefit	Innovative
Roctavian (valoctocogene roxaparvovec-rvox)	V	Hint for a non-quantifiable added benefit	AIFA procedure ongoing
Spherox (spheroids of human autologous matrix-associated chondrocytes)	SMR insufficient	Classified by the G-BA as a medical procedure	Not Innovative
Strimvelis (autologous CD34+ enriched cell fraction)	Not assessed by HAS	Not assessed by the G-BA	Formerly Innovative*
Tecartus (brexucabtagene autoleucel)	V	Hint for a non-quantifiable added benefit	Innovative (MCL) Conditionally innovative (ALL)
Upstaza (eladocagene exuparvovec)	III	Hint for a non-quantifiable added benefit	Innovative
Yescarta (axicabtagene ciloleucel)	III (DLBCL, PMBCL)/ V (FL)	Hint for a non-quantifiable added benefit/ No added benefit	Innovative (HGBL), Formerly Innovative* (r/r DLBCL, PMBCL). Not innovative (FL)
Zolgensma (onasemnogene abeparvovec)	III / V	No added benefit	Innovative

Diffuse large B cell lymphoma (DLBCL), Primary mediastinal large B cell lymphoma (PMBCL), Follicular Lymphoma (FL), Acute lymphoblastic leukemia (ALL)

*In Italy, the Innovative status (full or conditional) may last for up to 36 months

Clear benefit recognized | Non-quantifiable/some benefit | No benefit/innovation recognized

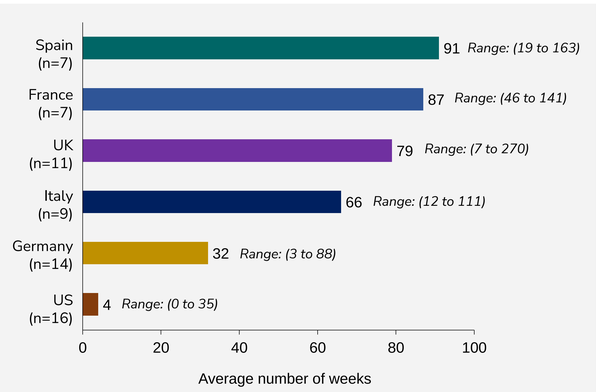
Figure 1: P&R procedural status of ATMP/cell and gene therapies approved and currently available in the US and EU4/UK (status as of Dec 31, 2023)



*6 of the 7 ATMPs undergoing negotiations in France are reimbursed via the early access scheme pending completion of standard P&R procedure

**All products undergoing negotiations in Germany are reimbursed pending completion of the procedure

Figure 2: P&R Average time to reimbursed access post regulatory approval in the US and EU4/UK (status as of Dec 31, 2023)



* Only therapies with positive P&R decisions included in the analysis for reimbursed access determination. Small sample size and outliers impact averages and should be interpreted with caution

CONCLUSIONS

- Cell and gene therapy space is growing with several products now on the market and an ever-evolving pipeline. However, patient access to ATMPs varies dramatically across countries.
- Visible ex-factory prices continue to set new records raising concerns about affordability and sustainability; the latest approved one-time gene therapy in the US (as of April 2024), Lenmeldy, launched with a WAC of $4.25M.
- In Europe, the gulf between visible ex-factory and net prices is continuing to widen, fuelling the debate on net price transparency across member states.
- Discussion is still open on the practical applicability of outcomes-based payment models and real-world evidence generation.
- Despite HTA bodies often criticizing the level of evidence provided, the value of cell and gene therapies is recognized at least in some cases. Especially with the planned adoption of the EUnetHTA joint clinical assessments (JCAs) framework for ATMPs by 2025, developments in the evaluation at the European and national levels will need monitoring.
- As additional ATMPs are added to the existing cohort we expect continuing evolution of attitudes and approaches.

^Therapies withdrawn US: Gintuit and Laviv ; *Europe: Maci, Provenge, Chondrocelect, Glybera, Zalmoxis, Zynteglo, Skysona*

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